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THE LIFE CYCLE OF PEPTIC ULCER *

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Notwithstanding years of intensive clinical study of the etiology, pathology, course and effects of treatment of chronic peptic ulcer, many points are still open for discussion. The advent of roentgenography has given a renewed impetus, opening up afresh, as moot questions, problems that apparently had been satisfactorily answered. The recent contributions of roentgenologists have tended to show that under favorable circumstances many ulcers tend to disappear and presumably to heal, the disappearance of the roentgenographic niche being the criterion on which such a judgment is founded.

On the other hand, the operation of subtotal gastrectomy for the radical removal of ulcer, an operation that seems likely to enjoy an increasing and a well warranted sphere of activity, has delivered into our hands fresh ulcer specimens of various types and at various stages in the life cycle of the peptic process.

These two factors alone have contributed considerable new information concerning the pathology, the course of the treated and of the untreated ulcer, the healing of the ulcer, and the conditions for its recurrence after incomplete cure. In the light of these new data, we may be privileged to reexamine the subject of the life history of ulcer, particularly from the standpoint of the healing of such a process after conservative medical, or after surgical, treatment. In particular, we are interested in the problem of what happens to a peptic ulceration in the stage of intermission of symptoms. Do ulcers ever spontaneously heal? Does an ulcer heal temporarily and partially when the patient enters a period of freedom from symptoms and the niche disappears? How often is such a healing process a durable and lasting one, and what are the pathologic stages in such a restitution to integrity? What are the conditions incident to the recurrence of ulcer? And, finally, to what extent do the usual surgical procedures vouchsafe lasting prevention of recurrence of the original or of new ulcers?

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From the mass of varied opinions, one fact seems to stand unchallenged, and that is that ulcers can and do heal. Stewart,[1] detailing the necropsy findings at the Leeds General Infirmary for the years 1910 to 1921, states that the "healing of gastric and duodenal ulcer is a common event." His statistics show that, in the postmortem room, scarring in the stomach is encountered almost as frequently as ulceration, while duodenal scars occur with about half the frequency of duodenal ulcers. Hart[2] found in general necropsy material in Germany that from 8 to 13 per cent. of adult bodies carry either open ulcerations or scars of healed ulcers, the scars and the ulcers occurring with about equal frequency. These statistical data are corroborated by many of the most representative pathologists, including Aschoff. We are therefore bound to accept the fact that, under satisfactory conditions, ulcers can and do heal in a certain percentage of cases. It remains for us to reexamine our material and to determine the required conditions for bringing about such a desired termination. But necropsy material is unsatisfactory in that it represents only an end stage of an ulcer or often an ulcer found accidentally during an examination in a case in which death has been due to some intercurrent disease. The gastric symptoms are in the background, probably not observed or noted, and new clinical knowledge of the life cycle of ulcer is not easily deducible.

On the other hand, in all clinics in which the operation of subtotal gastrectomy is being performed for ulcer, we have at hand many fresh specimens of ulcer removed at various stages in the cycle of life of the process, for instance, at the height of an attack, or after hemorrhage, or during the intermission stage, or just at the beginning of a recurrence. This constitutes today most valuable material for a review of the whole subject, and in many of the clinics of Europe (Askanazy,[3] Perman[4]) where such material has come to hand, such studies have been begun.

We have been so fortunate as to have had the privilege of prosecuting such investigations. The material at our disposal consists of approximately seventy specimens, each specimen consisting of the distal one third or one half of the stomach and adjoining first portion of the duodenum, including the ulcer itself. By correlating the clinical history with the pathologic picture of the ulcer, by bearing in mind the roentgen-ray evidence of healing, and by observing the incidence and frequency of recurrence of ulceration, we can add further valuable data to that at hand.

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1. Stewart, M. J.: Brit. M. J. **2**:1164 (Dec. 16) 1922; ibid. **2**:955 (Nov. 24) 1923.
2. Hart: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:291, 1918-1919.
3. Askanazy: Virchows Arch. f. path. Anat. **234**:111, 1921.
4. Perman, E.: Acta chir. Scandinav. **55**:286, 1923.

In addition, the medical wards of the hospital and the follow-up system in the outpatient department have given us ample and rich opportunity to observe, if only for a limited time up to date, the end-results of medical treatment. Clinical medicine and medical and surgical therapy being represented and pieced together, the sum total gives a good impression of the life history of a peptic ulceration.

PATHOLOGY OF A GASTRIC ULCER COMPARED WITH ITS CLINICAL HISTORY

If we study the specimens of gastric ulcer from cases in which there has been absolutely no previous gastric complaint and in which the history is of only a few weeks' duration, the onset of the symptoms abrupt, with severe pain, vomiting and rapid loss of weight, we are led to the belief that such typical peptic ulcer can and does form within a few weeks. The shortest history of such a case in our experience is three weeks. The ulcer in this instance was approximately 1 by 3 cm. in diameter, and had all the appearances of a chronic penetrating ulcer (Fig. 1); it had undermined edges, thickened walls, and its base was constituted of a thin remaining layer of muscularis and the slightly thickened serosa. Grossly and microscopically, in size and in shape, it had every characteristic of a penetrating peptic ulcer of long standing, except that there was little evidence of dense, cicatricial, connective tissue proliferation. Another ulcer, of four weeks' duration, had achieved a size of 2 by 3 cm., and represented a large crater with overhanging edges, a typical Cruveilhier ulcer.

Another group of specimens studied were those in which remissions alternated rapidly with attacks. In all of these cases, the recent history was one of almost continuous severe complaint without relief. These ulcers all ranged in size from 1 to 1.5 cm., and had an appearance identical with those in the previous group. There was no evidence of healing (Fig. 2).

From these two groups of specimens, we are led to believe that ulcers form rapidly, probably within two or three weeks, and, having by that time achieved a given size, no longer extend their circumference. They react only by an increase in protective connective tissue in the periphery and in the depths. This also would agree with the idea that perforation as well as hemorrhage usually are observed in cases with a history of only a few days or a week, namely, in the stage of rapid penetration. A far smaller percentage of chronic indurated ulcers of long standing give rise to sudden surgical perforation with peritonitis.

The largest ulcer we have seen, one that was 1.5 by 3.5 cm. in diameter, occurred in a man whose history was that of one year of continuous severe gastric complaints without intermission (Fig. 3). It

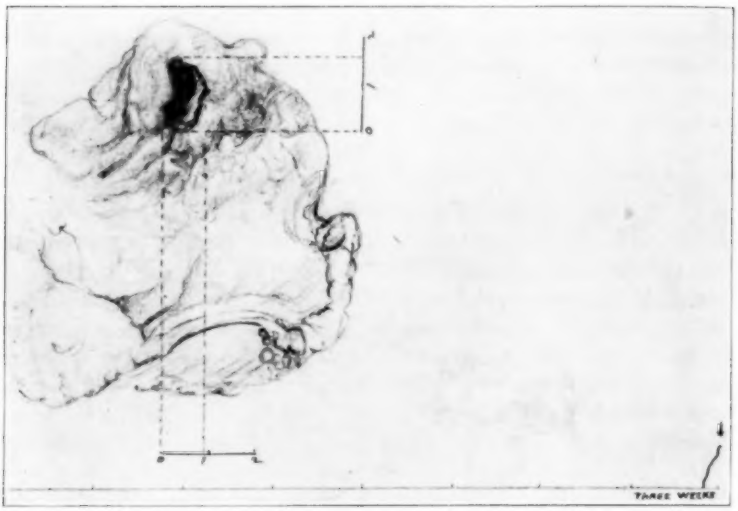

Fig. 1.—Penetrating ulcer of lesser curvature, deep, punched out, 1.5 by 1 cm., with sharp edges, muscularis base and marked induration. The patient, a man, aged 38, with no previous history of ulcer, began, three weeks before operation, to have severe epigastric pain one-half hour after eating. He had vomited once or twice and lost 15 pounds (6.8 kg.) in weight.

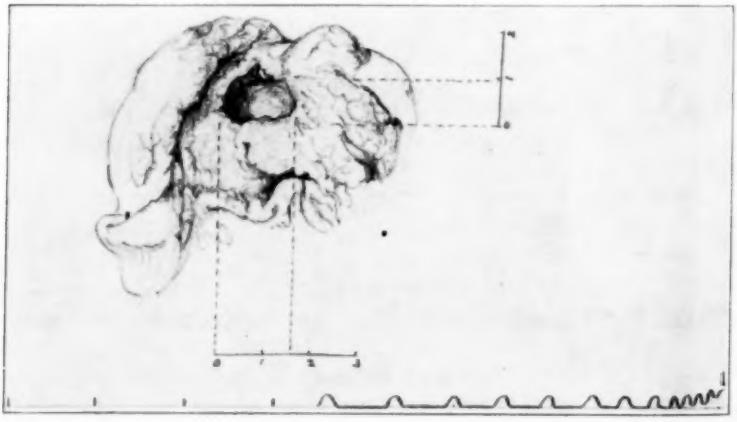

Fig. 2.—Penetrating ulcer of lesser curvature near pylorus, punched out, with overhanging edges, 1.5 by 2 cm.; muscular coat showing in the depth; blood vessels exposed. The patient, a man, aged 50, with a history of many years of typical gastric symptoms, had been much worse during the last few months, suffering a marked loss in weight.

is important to note that ulcers with continuous symptoms are larger, deeper and more dangerous than those in the preceding class in which attacks alternate with free intervals. A priori, one would surmise that in the intermission period a sufficient reparative process often takes place to prevent an extension of the pathologic ulceration.

In addition to this, there is a group in which the history was one of years, but in which long periods of freedom from pain were followed by shorter spaces of periodic activity of the ulcer. These ulcers were small, usually 0.5 by 0.5 cm. in diameter, superficial, and apparently had a firm connective tissue bed. These are ulcers showing a tendency to slow cicatrization.

Finally, there is a group of specimens of hour-glass deformity of the stomach. The specimens have a history of from one to twenty years. An open indurated ulcer has perforated the viscus, the base of the ulcer being formed by a neighboring organ, usually the liver. The crater is wide open, the base patulous and fixed to the liver. The ulcer has not healed; it is unable to contract because its base is fixed and unyielding. The productive reaction on the part of the ulcer results only in a thick callous ulcer with connective tissue strands infiltrating the serosa and encircling the viscus (Fig. 4). The result is the bilocular deformity. There is evidence of much and continued tendency to heal, resulting only in more deformity and failure to fill the crater with granulations. This does not necessarily preclude eventual healing, but certainly delays it indefinitely.

PATHOLOGY OF DUODENAL ULCERS COMPARED WITH THEIR CLINICAL COURSE

Duodenal ulcers have more of a tendency to be cast in one mold. Most of those seen in specimens removed at operation are smaller, about 0.5 by 1 cm. in diameter, rather shallow, with muscularis as a base, and show little tendency to productive cicatricial repair. In the case with the shortest history, four months, a fully developed ulcer was noted.

However, in the cases in which the intervals in the history have been longer than the periods of pain, a heaping up of inflammatory scar tissue may be distinctly seen. The largest ulcers were those in which the recent course, or the course from the onset, had been the most severe and the most continuous. Secondary diverticulum formation, as described by Akerlund,[5] is very common. It is in the nature of a pulsion diverticulum and occurs between the site of the ulcer and the pyloric sphincter. It occurred in every fourth or fifth specimen removed at operation.

5. Ackerlund: Roentgenologische Studien Uber den Bulbus Duodenum, 1921.

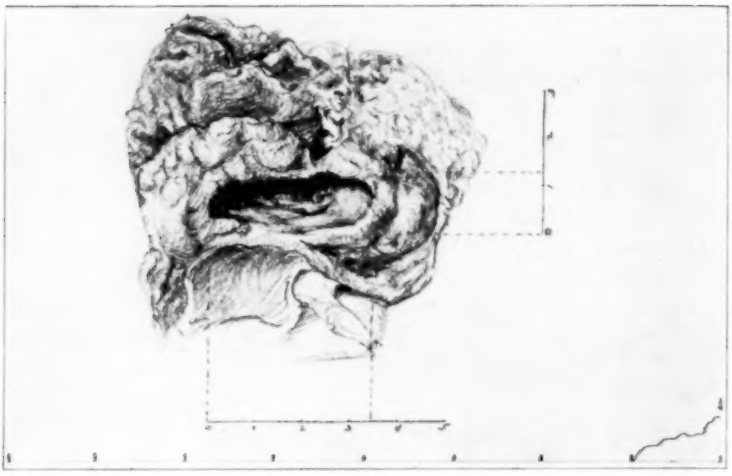

Fig. 3.—Large, oval, callous perforated ulcer at reentrant angle on lesser curvature. The patient, a man, aged 65, had a history of constant pain of increasing severity, of one year's duration, with marked exacerbation during the last two weeks, marked by severe pain and vomiting.

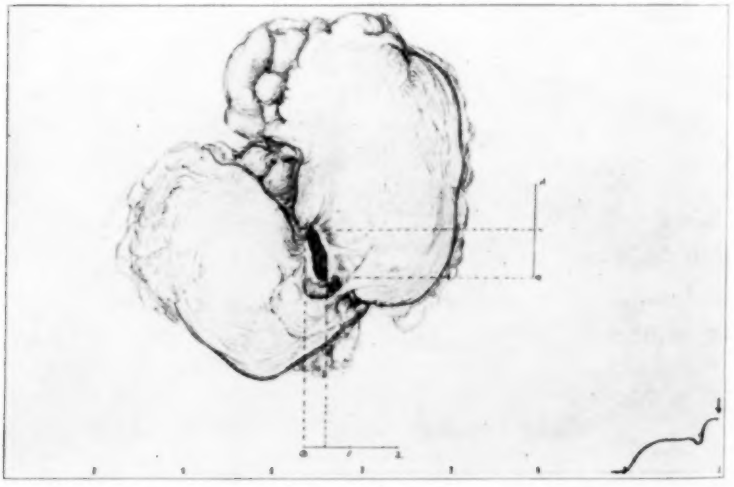

Fig. 4.—Specimen from subtotal gastrectomy for hour-glass stomach. The patient, a woman, had had symptoms for one year of epigastric pain, beginning twenty minutes after eating and lasting from two to three hours, which were relieved by bicarbonate. One month before admission, the pain became more severe and constant, and the patient lost 15 pounds (6.8 kg.) in weight. A test meal showed a high gastric acidity.

In a case of three years' duration in which the free intervals had been as long as six months, a small, puckered but open ulcer, 0.2 by 0.6 cm., was all that remained of the original ulcer. A large diverticulum was present between the ulcer and the pyloric sphincter (Fig. 5). The small size of this ulcer, in comparison with the long history, speaks for a well advanced reparative process. In another

Fig. 5.—Penetrating ulcer of duodenum, with secondary diverticulum formation, small, scooped out, 2 by 4 mm. The patient, aged 37, had had pains for 3 years at irregular periods, with remissions as long as six months. The present attack began three weeks before.

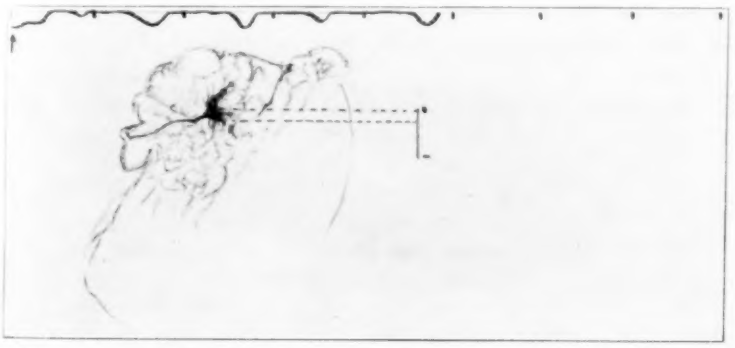

Fig. 6.—Simple duodenal ulcer. The patient had cramps of five years' duration, the attacks being mild with long intervals of remission.

case, of twenty years' duration, with mild intermittent symptoms, the ulcer was only 0.3 by 0.5 cm. in diameter. Again, a very large diverticulum was present. Apparently, the diverticulum was associated with cicatricial contracture in the walls of the ulcer.

Two cases, with five and twelve year histories in which there were periods of relief up to one year in duration, showed only a small, puckered ulcer, 2 by 3 mm. in diameter, with a shallow base (Fig. 6). Let

us not be understood to say that these ulcers had healed; there was a distinct, persistent loss of community of the surface mucosa, but there was also undoubted evidence of connective tissue repair taking place and contracture of the walls of the ulcer, both in depth and in circumference.

There remains for consideration a group of seven cases of duodenal ulcer in which, at the time of operation, the ulcer had either healed, pathologically speaking, or almost healed. This group was most interesting. The operative indications were clear cut. Most of these were cases in which a severe hemorrhage, endangering life, had occurred a few weeks previously. One was a case of recurring gastric tetany; and one was a case of repeated recurring ulcer attacks, in which the patient pleaded for permanent relief by surgical intervention. The cases in which profound hemorrhage almost to exsanguination had occurred were allowed several weeks in which to permit the regeneration of the blood elements and of the general strength of the patient. Following hemorrhage, it is almost a uniform rule that the gastric symptoms cease for a longer or shorter period. A modified Sippy diet was administered during the weeks following the hemorrhage. In the specimens removed at operation, the remains of the ulcer could usually be identified only as a small scar or a puckered area with regenerated mucous membrane. The same held true for the case of tetany.

The duration of the clincal symptoms does not seem to be of great significance, for some of these cases were five years or more in duration; the attacks, however, alternated with long periods of relief from symptoms.

The tendency of gastric ulcers to heal after hemorrhage is much less marked. Specimens of gastric ulcer after hemorrhage still show evidence of the erosion of the bleeding vessel in the base of the ulcer, and little in the nature of reparative reaction is visible.

In the phenomenon of the healing of duodenal ulcers after hemorrhage, one is faced by two contradictory facts. The ulcers show a definite tendency to heal and yet have given rise to severe hemorrhage. One can harmonize these facts only on the hypothesis that ulcers, or duodenal ulcers, heal readily in the intermission period, only to break down again and reulcerate with the next attack. It is only by such a hypothesis that one can explain such an apparent contradiction in facts. And yet, in this very phenomenon lies the explanation of what occurs in the intermission stage of the clinical history of ulcer, a tendency to heal followed by a reopening of the same or possibly of an entirely new ulcer with the next attack, another phase of healing and another recurrence of the ulceration. In some of these cases, final healing must take place, else we could not explain the postmortem discovery of gastric and duodenal scars. In probably a larger percentage of cases,

the extent and frequency of reulceration exceeds the phases of healing, until gastric surgery steps in and gives relief to the sufferer, or until a stenosis, or a fatal accident, hemorrhage or perforation, calls for operative cure.

This phase of healing and reulceration in the cases that are less amenable to medical treatment will again be discussed in connection with the roentgenographic evidence of the disappearance of the niche under medical treatment and its not infrequent recurrence. It is similarly seen in the healing of an ulcer after gastro-enterostomy, and in the not at

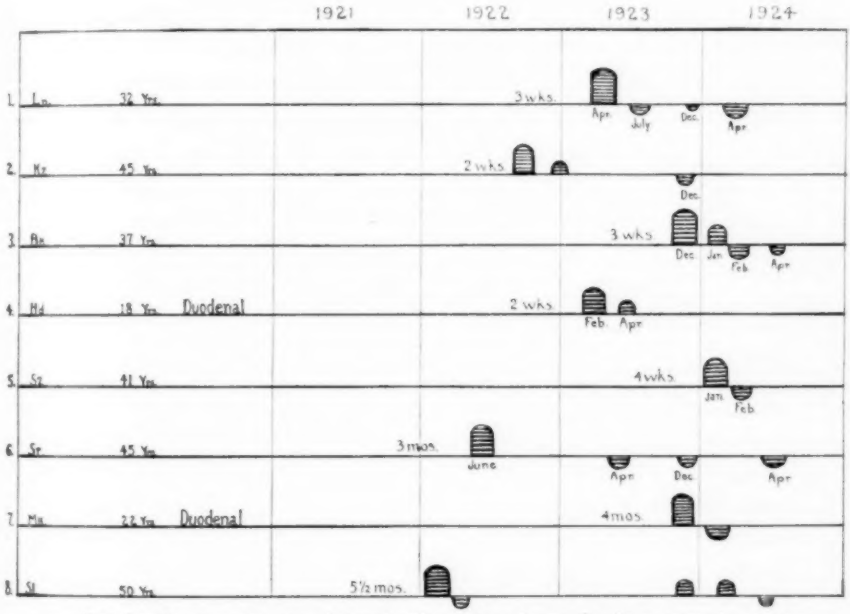
1921
1922
1923
1924
1. Lo. 32 Yrs. 3 wks. Apr. July Dec. Apr.
2. Kr. 45 Yrs. 2 wks. Dec.
3. An. 37 Yrs. 3 wks. Dec. Jan. Feb. Apr.
4. Hä. 18 Yrs. Duodenal 2 wks. Feb. Apr.
5. Sz. 41 Yrs. 4 wks. Jan. Feb.
6. Sr. 45 Yrs. 3 mos. June Apr. Dec. Apr.
7. Ma. 23 Yrs. Duodenal 4 mos.
8. Sl. 50 Yrs. 5½ mos.

Fig. 7.—Course of cases of penetrating ulcer observed with repeated roentgenographic examinations. In this and the succeeding charts, the elevation above the base line represents the observance of a "niche;" the depression below the line indicates a negative roentgenographic report. The elevations are placed approximately in the year and time of the year when the examination was made. The reference to weeks, months or years indicates duration of symptoms before first roentgenographic examination.

all infrequent recurrence of the same ulcer or of a new ulceration months or years after the apparent surgical cure.

OBSERVATIONS ON REPARATIVE PROCESSES IN PEPTIC ULCER

Until the cause of peptic ulcer is discovered, and until the lesion can be reproduced in experimental animals at will, the pathologic details of

repair cannot be completely followed. It may be safely assumed, however, that the characteristic features of the ulcer are the result of two opposing influences: (1) the causative, destructive factors which continue to operate, and (2) the protective reaction of the organism, the reparative factors. The histologic appearance of any individual ulcer, therefore, would seem to depend on which of these two influences is in the ascendant at the time the lesion is removed.

Specimens of approximately seventy-three partial gastrectomy operations during the last three years, performed for ulcer by Dr. A. A.

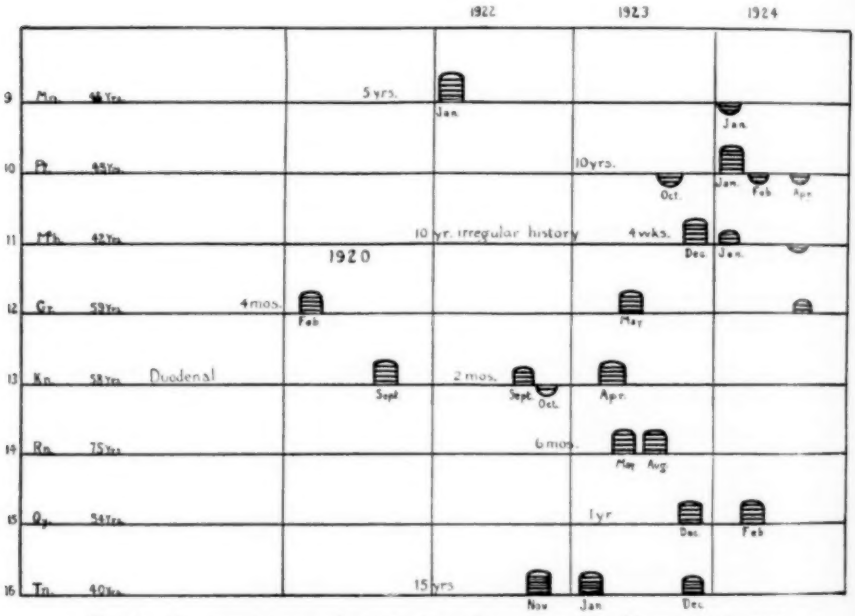

Fig. 8.—Course of cases of penetrating ulcer observed with repeated roentgenographic examinations.

Berg or members of his staff, have been reviewed to determine, first, the histologic features of reparative processes, and, second, the frequency of their predominance. It should be pointed out that evidence of such predominance does not prove that the process would have gone on to completion in any individual instance.

In thirty-four specimens of gastric ulcers, there was no specimen in which healing was predominant. The lesions showed, in general, the characteristic picture of ulcer as described by Askanazy [3] and Perman.[4] The mucosa about the ulcers showed inflammatory changes of the stroma, deformation and cystic dilatation of the glands, and an abrupt

loss of substance at the site of the ulcer. The latter presented an area of exudate overlying a zone of necrosis. The exudate consisted of mucus, fibrin, desquamated cells, leukocytes and round cells. The necrotic zone appeared to be granulation tissue or connective tissue, which stained poorly and was degenerated and infiltrated with round cells and polymorphonuclear leukocytes to varying degrees. Beneath this was a more or less developed zone of granulation tissue, and, lastly, a zone of dense connective tissue from which capillaries passed into the zone of granulation tissue. The muscle bundles of the stomach, which were broken through in all but three instances, showed a varying degree of infiltration by round and plasma cells. The large vessels in the base of some penetrating ulcers showed closure by thrombus, or granulation tissue replacing the thrombus.

Two specimens of pyloric stenosis and two of hour-glass deformity showed active ulcers with no evidence of healing. The dense scar

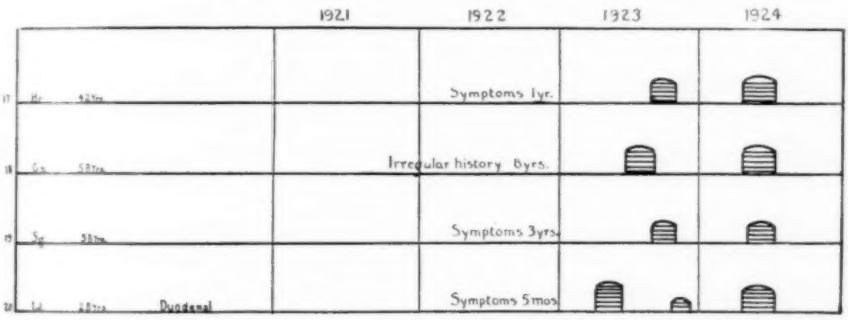

Fig. 9.—Course of cases of penetrating ulcer observed with repeated roentgenographic examinations.

tissue forming the outer layer of the lesion represents a protective reaction of the organism but does not seem to aid repair of the ulcer itself. In fact, by pinching off the blood vessels and nerves it may conceivably interfere with repair.

In thirty-nine specimens of duodenal ulcer, however, eight showed convincing microscopic evidence of predominating reparative processes. While the active ulcers showed essentially the same lesions as the gastric specimens (although smaller in size and depth), these eight specimens showed no zones of exudate or necrosis. The defect in the mucous membrane, from 2 to 5 mm. in diameter or in the form of a narrow, elongated, puckered slit, was formed by delicate granulation tissue, which seemed to arise from the stroma of superficial glands and often had a papillary arrangement. In two instances, a single layer of epithelial cells was found growing from the glands of the adjacent

mucosa downward into the defect and covering the delicate granulation tissue. Beneath the healing ulcer, denser connective tissue and muscle bundles were found drawn upward toward the surface. The Brunner's glands were seen on either side, but they seemed to play no part in the process of repair, having apparently been destroyed at the site of the ulcer during the active stage.

Two specimens of small duodenal ulcers with diverticulum formation showed necrosis still going on in the ulcer. Here, as in hour-glass deformity, the protective connective tissue contraction had not tended to actual healing.

ROENTGENOGRAPHIC EVIDENCE OF COURSE OF PEPTIC ULCER JUDGED BY DISAPPEARANCE OF NICHE

During the last two or three years, we have had the opportunity of observing the roentgenographic behavior of a small group of gastric and duodenal ulcers. From the large mass of hospital material, we have

Clinical Improvement and Diminution in Size of Niche in Cases of Peptic Ulcer

Age	Good, Niche Disappeared	Improved, Niche Smaller	Unimproved, Niche Unchanged	Recurrence of Symptoms and Niche
From 20 to 40 years	3	1	1	0
From 40 to 60 years	7	1	6	2
Over 60 years	0	0	1	0

Duration of Symptoms	Niche Disappeared	Niche Smaller	Niche Unchanged	Recurrence of Niche
From 2 to 4 weeks	4	0	0	0
From 1 to 6 months	3	0	1	1
From 6 months to 2 years	0	0	3	0
From 2 to 10 years	4	0	5	1

chosen this group, because, small as it is, twenty in all up to date, each case has been continually under our clinical observation. In addition, we have had more than one roentgenographic examination during the attack, in the intermission period and, when the opportunity offered, at the onset of recurrent symptoms. In this way, we have been able to collect data and draw conclusions which can be compared with those deduced from the pathologic examination of resected specimens.

Occasional mistakes are undoubtedly made in which persistent peristaltic waves, overlying shadows of barium filled intestines, perigastric adhesions or localized spasms give a false impression of a penetration from within the viscus. In general, it may be said that the disappearance of a visible roentgenographic niche, as a sign of a penetrating ulcer, runs parallel with the clinical improvement in the course of the case, just as reappearance of the roentgen-ray evidence of the penetration occurs simultaneously with the recurrence of active symptoms.

Several competent observers have hesitated to accept the disappearance of the niche as a sign of healing in an ulcer. Hollander [6] reported a case in which the resected specimen showed an active ulcer though the niche was no longer present. Many have warned against interpreting every projection in the contour of the stomach, as outlined with opaque meal, as a certain evidence of a penetrating ulceration. One may allow for a percentage of error in the interpretation of the roentgenographic films, but the percentage is probably very small. Repeated roentgen-ray examinations in the same case at various intervals go a great distance in automatically controlling such errors. When one observes, in a fair number of cases, a definite parallelism between the clinical facts and the roentgen-ray evidence, one is sorely tempted to minimize theoretical objections and to consider the niche as a sign of ulcer and its disappearance as presumptive evidence of its healing.

Whether the disappearing penetration means a fully healed ulcer, a scar, or merely a filling of its crater with granulation tissue as a temporary stage toward the healing process remains for future studies to disclose. The thoroughness of the healing process, that is, the filling of the crater with new-formed connective tissue and the regeneration of the mucosa, undoubtedly depends on the length of the intermission period or the final permanency of the cure. Until some one is fortunate enough to be able actually to show the stomach of an individual in which an observed niche has disappeared, there will always remain some healthy doubt as to the exact significance of the phenomenon. The observation of this group of twenty cases with repeated roentgen-ray examinations has furnished the following data:

1. The niche disappeared completely in ten cases (Figs. 7, 8 and 9 and table), and partially in two additional instances. In eight of the twenty cases, neither the niche nor the clinical symptoms were beneficially affected by the course of treatment.

It may be that with a more persistent and more carefully supervised therapy the results would have been better. The refractory patients had all been referred to the hospital wards and had received bed rest, alkalis and a modified form of Sippy treatment. Ohnell [7] reports a far larger percentage of success in such cases, and Buscher [8] recently reported, in a series of 100 cases, seventy-one in which the niche completely disappeared; fifteen in which it diminished; eleven in which it remained unchanged, and three in which it disappeared only to reappear with the next attack of pain.

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6. Hollander, Edward: Fallibility of Roentgenologic Evidence of Healed Gastric Ulcer, J. A. M. A. **80**:29 (Jan. 26) 1923.

7. Ohnell: Acta med. Scandinav. **53**:706 (Jan.) 1921.

8. Buscher, J.: Arch. f. Verdauungskr. **31**:327 (July) 1923.

Our own small series includes some patients with the most difficult examples of chronic callous ulcer, such as are known to haunt for years the wards and outpatient departments of large city institutions.

2. Of the cases in which the niche either disappeared or diminished, four patients were between the ages of 20 and 40 years and eight were between 40 and 60.

It is a significant fact that all the cases of failure to influence the size of the niche and prevent recurrence occurred in persons aged 45 or more. Most of them were between 50 and 60 years old.

3. We are impressed with the fact that the shorter the duration of the symptoms at the time that medical treatment was begun, the better the chance for healing. Thus, all our cases in which treatment was instituted within from two to four weeks of the onset of complaints, four in number, reacted favorably with disappearance of niche and symptoms. Of four patients complaining from one to six months, three completely cleared up and one showed a persistent niche.

On the other hand, the impression is gained that cases with long standing histories give less favorable results. Of the twelve patients complaining from six months to ten years or more, in only four did the penetration disappear. In one additional case, the ulcer presumably healed but broke down within a month, the niche reappearing. The remaining seven chronic patients were not influenced by treatment. Considering these twelve chronic cases as a subgroup, we note that three of the four favorable patients were less than 45 years of age, while of the eight unfavorable patients six were more than 45 years of age.

Again analyzing these long standing cases, we see that those with long intermissions between attacks heal more readily. On the other hand, in patients that have long continued, intermittent attacks, with short intervals of relief, the ulcer can occasionally heal, particularly when the patient is not advanced in years.

4. The clinical course of gastric ulcer is further well exemplified in the instances in which apparent cure was followed by a recurrence of symptoms and a reappearance of the niche. In one case (Case 8), the niche disappeared and complete relief from symptoms was observed for eighteen months. The patient returned to the clinic with recurring symptoms only slightly over one week in duration. An immediate roentgen-ray examination demonstrated the niche to be already present. Hematemesis shortly ensued. A thorough course of medical treatment resulted in cessation of all symptoms and again in the disappearance of the roentgenographic penetration. In a second case (Case 13), complete relief from symptoms for six months was followed by reappearance of the niche and of clinical symptoms. These patients were aged 50 and 58, respectively. In another case, a penetrating ulcer of the lesser curvature

disappeared under medical treatment, the patient feeling well for some months. A recurrence of symptoms for some days was followed by a sudden perforation of the same ulcer. A subtotal gastrectomy resulted in cure.

From a study of such cases, one is led to the conclusion that peptic ulcers probably heal under medical treatment, healing being more successful in younger persons and in those with a short clinical history. Healing also is possible in protracted cases in which the free intervals are long in duration and the attacks mild. If one assumes with Ohnell that forty and one-half days is the average length of time necessary for the disappearance of the niche and, hence, for healing, then all the cases in which the free interval is more than six weeks in duration have a greater predisposition and tendency to heal. Cases in which the symptoms are continuous or in which the intermission periods are less than six weeks, represent chronic callous, unhealing ulcerations.

Unfortunately, such physiologic healing is not always permanent, for reulceration may take place, and thus, as in Case 8 of this series, one sees exemplified the rather customary history of ulceration followed by disappearance of the niche, a long free interval and again ulceration, to be again followed by disappearance of the penetration. In both these cases, the niche reappeared at approximately the same point on the gastric wall as on the previous occasion, from which one might deduce that the so-called healed ulcer remains as a *locus minoris resistentiae*, evidencing a tendency to break down again and form a new ulcer in the same scar or in the granulating wound of the previous ulcer.

THE BEHAVIOR OF PEPTIC ULCER IN THE STOMACH WHICH HAS BEEN OPERATED ON

Those who are privileged to study and observe the behavior of peptic ulcer after operation will find in this opportunity a wealth of material which throws much light on the life cycle of ulcers. That ulcers can and do heal after simple gastro-enterostomy is amply demonstrated, not only by a fair percentage of clinical cures after such an operation but also by necropsy observations, made years after, of patients whose death has been due to some intercurrent disease. Surgeons who are forced to open the abdomen in such cases for secondary causes often find the scars of such healed ulcerations. Just what percentage of gastric or duodenal ulcers are cured by gastro-enterostomy remains today a much mooted question, the percentages reported by various surgeons ranging from 30 to more than 90 per cent. and depending to a great extent on the thoroughness with which the follow-up has been prosecuted and the open-mindedness or the bias of the critical observer. That gastro-enterostomy is a sure cure for all cases is, however, being

more and more questioned. The best example of the constitutional tendency continually to recreate ulcers in the same or in new situations in the gastric wall is to be seen in the cases of recurrence of the original ulcer months or years after gastro-enterostomy, and in that large and increasing problem of what to do for gastrojejunal and jejunal ulcers. It is not unlikely that most ulcers, particularly duodenal ulcers, heal at least partially after such an operation, for, in the largest percentage of cases, an interval of freedom from symptoms and apparent cure follows the surgical procedure. On the other hand, the not inconsiderable percentage in which this period is followed by one of recurrence of all the symptoms, including hemorrhage, bears mute witness to the fact that many such ulcers either heal incompletely or heal only to break down again in spite of the anatomosis. Years may elapse before the recurrent ulceration occurs; in one of our cases as long as six years intervened, but the tendency to recur is there nevertheless.

The recurrence of a lesser curvature ulcer after cautery or knife excision is another not infrequent manifestation of the constitutional tendency of an ulcer to reform in an imperfect scar. The impressive problem of the gastrojejunal ulcer looms larger daily. It is variably estimated that gastrojejunal ulcer occurs in from 2 to 16 per cent. or more of all cases of gastro-enterostomy for ulcer. The high mortality in secondary operations for the relief of such secondary ulcerations makes this chapter of gastric surgery one demanding much serious attention, particularly from the point of view of preventing its occurrence.

The stories of some of the lamentable subjects of repeated surgical operations are very valuable when viewed from the angle of the life cycle of the ulcer and its underlying ulcer bearing constitution. One type of case is that in which, following a palliative gastro-enterostomy, the original gastric or duodenal ulcer heals but a new gastrojejunal ulcer forms. Another type of ulcer is that in which reperforation of the same ulcer has been noted years after the original operation. Still another group, though small, is that in which the original duodenal or gastric ulcer heals after gastro-enterostomy, but some time later operation is required for a chronic callous ulcer elsewhere in the gastric wall. Similar is the group in which, following the excision of a gastrojejunal ulcer, a second gastrojejunal ulcer forms. But the most interesting group from the standpoint of reulceration and healing is the following:

This group comprises three cases in which gastro-enterostomy had been performed for a gastric or a duodenal ulcer. Following this expedient, renewed symptoms required relaparotomy. At such a second operation, the original ulcer (lesser curvature of stomach or duodenum) was seen to be entirely healed, but a gastrojejunal ulcer had formed. In view

of the fact that the original ulcer had healed, the gastro-enterostomy was undone, and the original physiologic condition restored. Sometime subsequently, renewal of severe symptoms led to a third laparotomy, at which operation it was noted that in all three instances the primary ulceration had recurred, and in the identical site. In the case with the lesser curvature ulcer, it had recurred on the latter curvature and both duodenal cases showed renewed duodenal ulcerations. These examples are profoundly striking in that they show that, even though an ulcer is apparently well healed after a gastro-enterostomy, a return to normal conditions again brings into play the factors that had created and will again create the original ulcer.

Subtotal gastrectomy removes the ulcer bearing area of the mucosa of the stomach and the first portion of the duodenum, and leaves an anacidity permanently established in the remainder of the viscus. Since one cannot operate on the constitution of the patient, it would seem to be advisable, in the interest of the patient, to perform such a surgical procedure as will guarantee removal of not only that ulcer but also the milieu for the recurrence of a new one. This, subtotal gastrectomy seems to do.

SUMMARY

1. Chronic peptic ulcers may form within two or three weeks of the onset of symptoms. This conclusion is based on the history of the patient, the observation of the recurrence of a niche within two weeks of recurrence of the symptoms, and, finally, on the ease with which such short timed ulcers can be made to disappear under medical treatment (from ten days to two weeks).

2. Chronic ulcers achieve their maximum size within a few weeks and do not thereafter extend their borders.

3. Pathologic and roentgenographic evidence indicate that healing in the intermission stage does progress. The degree of healing and its permanency depends on various factors. The younger the individual and the shorter the history, the greater the tendency to healing. Cases with long intermission periods and with mild attacks heal more readily than those with continuous active symptoms. An ulcer in a person over 45 years of age can heal only with difficulty.

4. Histologic evidence indicates that healing takes place by the filling of the crater of the ulcer with firm granulation tissue, by retraction of the muscularis, by contracture of the opening and by regeneration of the mucous membrane. We have no pathologic specimen of gastric ulcer in which complete healing has taken place. We have several specimens indicating the healing of duodenal ulcers in the intermission stage.

5. Cases of duodenal ulceration in which there has been hemorrhage seem to heal most readily.

6. Neither pathologic evidence of healing nor roentgenographic demonstration of the disappearance of the niche is to be considered as proof of clinical cure. Ulcers may readily heal in the intermission stage but, unfortunately, show a tendency to break down again, probably at the same site. A certain number of ulcers eventually heal completely; others do not, and these become surgical cases.

7. The mishaps after gastro-enterostomy furnish many illustrations of the constitutional tendency of ulcers to reform in the same or in new sites of the stomach wall. Thus, recurrence in situ after local removal, recurrence of the original ulcer after apparent healing resulting from gastro-enterostomy (the large number of gastrojejunal ulcers) and, finally, the recurrence of the original healed ulcer when the gastro-enterostomy must, for some reason, be undone—all these point to the advisability of performing such an operation for ulcer as shall remove not only the ulcer but also the ulcer-bearing mucosa, namely, the operation of subtotal gastrectomy.

GASTRIC MOTOR ACTIVITY IN PATIENTS WITH PEPTIC ULCER*

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In any report of experimental work on chronic peptic ulcer, the method of arriving at a diagnosis of ulcer is important. I chose twenty-nine patients who presented: (*a*) carefully elicited clinical histories of attacks of regularly recurring epigastric distress with definite relation to meal taking; (*b*) relief from pain by eating, by emptying the stomach and by alkalis (all of these repeatedly demonstrated during a ten or fourteen day period of hospital observation while on a diagnostic "test-out"),[1] and (*c*) complete relief from pain while on ulcer treatment. This lasted for four weeks in the hospital and continued for months at home. (The follow-up on these patients extends over from one to two years in the Sippy routine.)

The above named conditions (*a*, *b* and *c*) were all characteristically present in the twenty-nine patients. In addition, (*d*) a number had gastric peristaltic waves and other evidence of chronic obstruction at the

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*The work on twenty-nine patients reported here was begun at the suggestion and under the supervision of Dr. B. W. Sippy, several years ago, when the writer was doing postgraduate study on the service of Dr. Sippy in the Presbyterian Hospital of Chicago. The clinical material at my disposal during these years was abundant. Therefore, only such patients as were found peculiarly adaptable to the experimental work were selected for the study. Private cases, largely those of Drs. B. W. and A. F. Sippy, were used.

1. In the Sippy routine of gastro-intestinal diagnosis, patients are subjected to rigid preliminary observation and study in the hospital. The distress that develops during this period of observation is carefully analyzed and shown to be consistent with the distress of ulcer before a diagnosis of ulcer is made. For example, it is actually determined that when the distress attributable to ulcer does appear, it comes on an appreciable time after eating an ordinary meal and not while eating or immediately after eating, but usually from one to three hours afterward. It is also determined that the distress is relieved in a characteristic manner by a small meal, consisting of two eggs, a cereal, two glasses of milk and some bread and butter; likewise, by the administration of adequate quantities of alkali or other chemical agents that have acid neutralizing properties. On other occasions when the distress is at its height, or when distress is present at a time when the stomach normally should be empty, a stomach tube is used to ascertain if food and gastric secretion, in quantity and quality compatible with a diagnosis of ulcer, are present in the stomach and if the emptying of the stomach gives characteristic relief to the pain. The painstaking accuracy with which a diagnosis of ulcer was made by Dr. Sippy was recognized by all who observed his work, and can be surmised by those who read his scientific articles.

outlet, such as is obtained by finding a retention on motor meals, or sarcinae in stomach contents; (*e*) a number had blood in the stools which disappeared later on ulcer management, and some gave a history of hematemesis; (*f*) twenty-three of these patients showed unmistakable duodenal or gastric defects typical of ulcer by roentgen-ray examination, and nine of them were proved at operation. The rest showed suggestive roentgen-ray findings or were unsatisfactory because of poor visualization of the duodenum, due to its position.

Recently, reviewing the hospital charts of these patients, it seemed reasonable to believe that the diagnosis of peptic ulcer would remain unquestioned by medical and surgical clinicians versed in the diagnosis

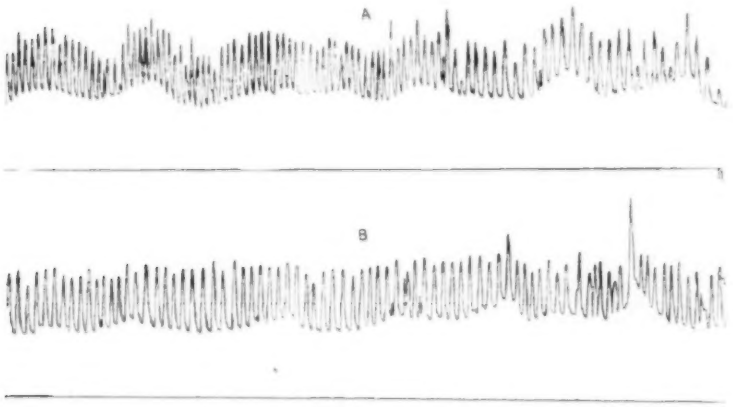

Fig. 1 (Case 1).—*A*, peristalsis, during pain period, before alkali administration; at the two signals on base line, pain was momentarily aggravated; *B*, type of peristalsis, when pain had completely disappeared, following alkali administration.

of ulcer, because of the combination of signs and symptoms in the patients used for the work.

The investigation was conducted as follows: A patient previously diagnosed as suffering from peptic ulcer was studied during an attack of typical pain. At the onset of pain (as a rule from one to three hours after eating), the patient swallowed a small balloon, such as is ordinarily used to record gastric peristalsis in the method developed by Dr. A. J. Carlson. Dr. A. Luckhardt of the department of physiology at the University of Chicago gave helpful suggestions on the technical side of the investigation. The balloon is connected by means of rubber tubing to an air-bromoform manometer, which, through a rising and falling pointer, records intragastric changes in pressure on the smoked paper of a revolving drum (kymograph). Cardiac beats and the respi-

rations are superimposed on the gastric peristalsis by this method. The record of stomach peristalsis was continued for from one to one and one-half hours. Patients were asked to record any changes in pain, either increases or decreases, through an electric magnet. As a rule, the pain continued steadily or gradually increased, rarely decreasing in severity for over one-half hour. At that time, with the balloon in situ, patients were given by mouth chemical neutralizing agents in sufficient dosage to neutralize stomach acidity, usually from 30 to 60 grains (1.9 to 3.8 gm.) each of sodium bicarbonate and calcium carbonate. The tracing was continued without artificial change of pressure in the balloon system (except in a few for accidental reasons) for thirty or forty minutes longer.

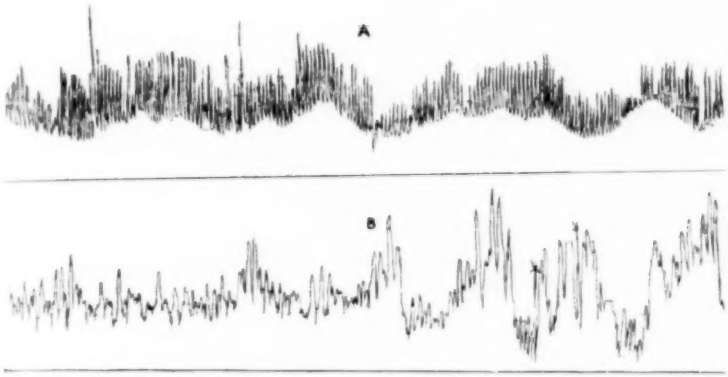

Fig. 2 (Case 2).—*A*, type of peristalsis, when pain was quite severe, before alkali administration; *B*, after alkali administration, when pain was gone.

It was originally planned to have patients swallow a Rehfuss tube as well as the balloon, simultaneously to check the acidity, but it was early demonstrated that the effort to swallow the balloon during an active pain period tended to make these patients vomit, so we abandoned the Rehfuss tube. Since we were primarily interested in the peristalsis, not in the acid figures, at from two or three to ten hour intervals following ordinary meals, we were content with knowing that all these patients had had high free acid findings on other occasions, as shown by Ewald, motor meals, and aspiration. At the end of the tracing, practically all the patients were aspirated. Usually the contents withdrawn contained food eaten at the previous meal, and the majority showed no free acid with dimethylaminoazobenzol, indicating that enough neutralizer had been given to control free acidity from the time of administration to the end of the tracing.

RESULTS

1. Of twenty-three tracings made during active distress periods, although the pain was invariably completely relieved after giving the neutralizer, (*a*) nine showed no change in peristalsis after the soda bicarbonate and calcium carbonate were given; (*b*) ten showed varying increase of peristaltic activity after the neutralizer; (*c*) three showed decreased peristalsis after the neutralizer, and (*d*) one showed decreased peristalsis for twelve minutes and then increased, beyond the prealkali period.

2. Of two tracings made during active distress periods in which the neutralizer did not relieve the pain completely, both showed no peristaltic change after the soda bicarbonate and calcium carbonate.

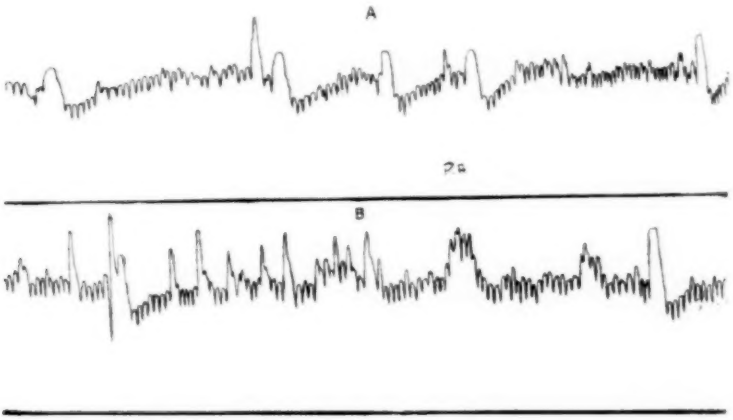

Fig. 3 (Case 3).—*A*, peristalsis, when pain was present, before alkali administration (*PA*, pain momentarily aggravated); *B*, when pain was gone, after alkali administration.

The distention caused by the carbon dioxid gas, formed in quantities from the combination of hydrochloric acid with the large doses of neutralizer used, undoubtedly made it difficult for the patients to distinguish the last remnants of the typical ulcer distress from the discomfort caused by the distention. Without this overdistention of the stomach, Dr. Sippy demonstrated that distress attributable to ulcer, unassociated with pain producing complications, such as perigastritis, is invariably completely relieved in from five to fifteen minutes by an adequate quantity of neutralizer. In the future, it is planned to give calcined magnesia, which liberates no carbon dioxid, together with smaller doses of carbonate in place of the large doses of soda bicarbonate and calcium carbonate used in these experiments.

3. Of four tracings taken during distress free periods in ulcer patients, two showed an increase of peristalsis following a neutralizer; the other two showed no change.

4. Nineteen showed no change in general tone following soda bicarbonate and calcium carbonate (as measured by the average distance of the tracing from the base line). In the remaining ten, there were artificial interruptions requiring small changes in the air-bromoform apparatus.

CRITICISM

It is ideal to check the acidity and peristalsis simultaneously throughout the experiment. This was not accomplished because human beings in pain make poorer experimental animals than pain free human beings, and untrained patients poorer experimental animals than trained laboratory workers, man or dog.

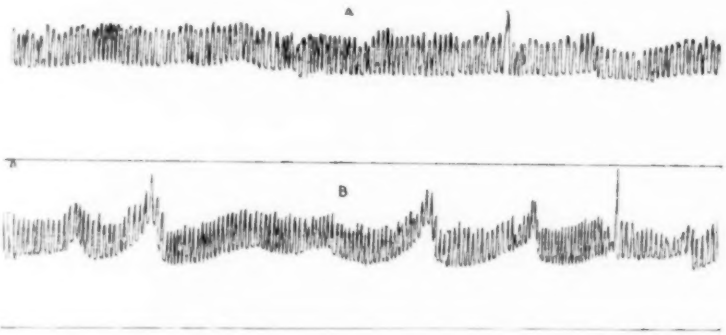

Fig. 4 (Case 4).—*A*, peristalsis, when pain was severe, before alkali administration; *B*, when pain was gone, after alkali administration. When the acid findings were concomitant, the peristalsis showed: *(a)* a moderate but definite increase after alkali, and *(b)* no relation to severity, mildness or absence of distress. Free acid was highest when the pain was severest, lower when the pain was mild, and absent when the pain was gone. The findings were: 6:43 p. m., severe pain, very low tonus, free hydrochloric acid 95; 6:52 p. m., pain mild, long tonus waves, free hydrochloric acid 44; 7:03 p. m., pain mild, long tonus wave, free hydrochloric acid 50; 7:10 p. m., pain gone, second type peristalsis, free hydrochloric acid 0; 7:43 p. m., pain absent, low tonus wave, and free hydrochloric acid 0.

The balloon in the fundus method does not record the entire peristaltic cycle. Reynolds and McClure of the Peter Bent Brigham Hospital, in 1922, stated that "the balloon method does not accurately record fluoroscopic observations." This method cannot record all that is going on in the stomach, such as double or triple peristaltic contractions, or local or pyloric spasms. It is admitted that it records changes of pressure in the fundus. Indeed, it records very delicate changes in pressure in the fundus, as is shown by its record of the heart beats against it. Prepyloric contractions may not cause changes of pressure in the fundus sufficient to register through the balloon, but it seems

probable that they do. It is likewise difficult to see how any peristaltic wave traversing the antrum would fail to register on the balloon.

Lastly, we must be careful in drawing conclusions as to the actual factor responsible for the varying changes in gastric peristalsis which were observed in sixteen of the twenty-nine patients following soda bicarbonate and calcium carbonate. Changes in types of peristasis during digestion may occur in normal and abnormal human beings at varying times when short records, such as these, are taken.

COMMENT ON MAIN THEORIES OF CAUSE OF PAIN IN PEPTIC ULCER

Before drawing conclusions from this series of tracings, it may be profitable to review briefly the chief theories of the cause of pain in peptic ulcer.

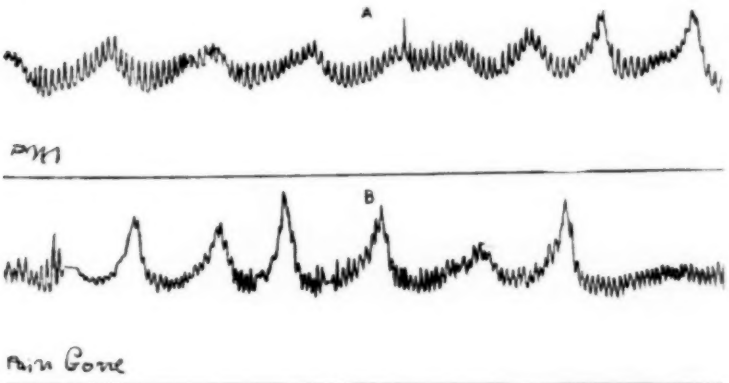

Fig. 5 (Case 5).—*A*, peristalsis, when pain was present, before alkali administration; *B*, when pain was absent, after alkali administration.

One conceives that the free hydrochloric acid has something to do with the pain when the ulcer is in an "irritable" state. This idea is founded on the universal observation that when the hydrochloric acid is reduced or completely neutralized by alkalis or food, or removed by emptying the stomach of food and secretion, the pain of uncomplicated ulcer disappears. The foregoing experiment neither proves nor disproves this theory.

Carlson, Ginsberg, Tampowski, Hamburger and Hardt have claimed that active peristalsis is responsible for the pain and that the alkali, by affecting peristalsis, gives relief of pain in ulcer. They have attempted to prove this by taking tracings on ulcer patients while the pain of ulcer is present and at other times when it is not present.

Drawing conclusions from his tracings, Carlson thought that the peristaltic contractions were felt as *pain* when the ulcer is in an "irritable state," while similar peristalsis might go on without conscious sensations at other times when the tissues were less irritable. His work was done on stomachs that were being aspirated at intervals through a Rehfuss tube, so that they contained no food and, at times, very small amounts of secretion.

Hardt believed that by demonstrating more active types of peristalsis during the pain periods in a few patients, he had proved that the peristalsis was the cause of the pain. Then Carlson, who had shown that many things, such as water, acid and alkalis, put into the stomach temporarily inhibited peristalsis, concluded by indirect reasoning that alkali stopped the pain of ulcer by inhibiting peristalsis. Not one of them has ever given quantities of alkali adequate to neutralize the free hydrochloric acid during an ulcer distress period when food and secretion were present in the stomach and noted the effect on peristalsis, as the writer has done. Only four of the twenty-nine patients reported in this study showed decreased peristalsis after the neutralizer, a result in no way justifying the theory of the foregoing workers.

Carlson has thought that "tonus," even of normal variety, is felt as pain when an ulcer is in the "irritable state." Why a neutralizer like calcined magnesia should allay this irritability in so perfect a fashion as it does and magnesium sulphate, which does not combine with hydrochloric acid, should not (both, in addition, being decided stimulants to the intestine) is a known fact difficult to reconcile with Carlson's interpretations.

Hamburger and Ginsberg have suggested that increase of tone is responsible for the pain and that alkali changes tone, but have offered no direct proof. This experiment shows that there is regularly no change of tone after the administration of soda bicarbonate and calcium carbonate.

Another theory is that localized spasm at the site of the ulcer is responsible for the pain of ulcer. No direct proof for this conception is at hand.

Spasm at the pylorous or first portion of the duodenum with "intensified tonus usually" is conceived to be responsible for the pain by the above mentioned workers, but again the proof, even a method for proof, is lacking. In roentgenographic observation, although hyperperistalsis, reverse peristalsis and irregular peristalsis are easily observed, it is very difficult to demonstrate pylorospasm, according to Reynolds and McClure, who reported a very thorough piece of radiographic work on

sixteen ulcer patients.[2] Pylorospasm, according to them, is always intermittent. They concluded that motor disturbances of the stomach or pyloric region are almost invariably associated with ulcer pain. In some of these cases, however, the peristalsis remained unchanged after the pain stopped or changed to abnormal type. There was, in other words, no such unfailing correspondence in change of peristalsis, during pain free periods, as there is unfailing relief of pain, when sufficient neutralizer is administered to an ulcer patient.

Any theory of motor phenomena as the cause of pain in ulcer, except that of continuous localized spasm, is at variance with the clinical observation that the distress of ulcer, when present, is usually continuous. The

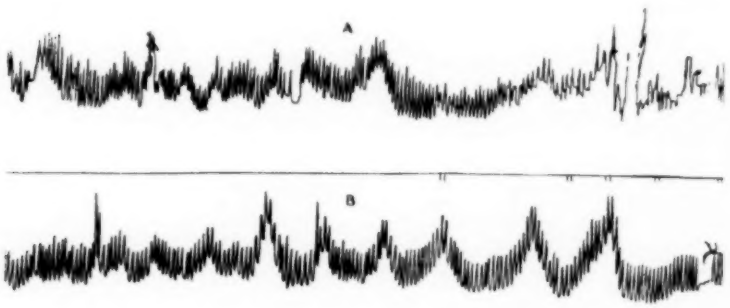

Fig. 6 (Case 6).—*A*, peristalsis, when pain was severe (the patient groaning) before alkali administration; signals on base line indicate that pain was especially aggravated at these points; *B*, peristalsis, when pain was entirely relieved, after alkali administration.

patient himself often describes his pain as gnawing or boring, not as a "spasm." That patients with peptic ulcer, during their severest pain periods particularly, have exacerbations of pain superimposed on the less acute but continuous distress is well known, however. One can conceive that these exacerbations might fit in with the periodicity of the peristaltic contractions. Hardt has shown tracings in which the patient signaled his greatest distress each time that the kymographic pointer approached the summit of a wave. In the tracings reported here, the patients were quite regularly unaware of these exacerbations at the height of the wave curve. In one tracing, there seemed to be fair

2. Reynolds, L., and McClure, C. W.: Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, Arch. Int. Med. **29**:1 (Jan.) 1922.

correspondence between the wave and exacerbations of pain. In another, in which probably the highest waves of any obtained were recorded, there was some correspondence, but there also were shown aggravations of pain without accompanying waves and vice versa. In still a third patient with very active peristalsis, the waves themselves were felt as a "turning over" sensation in the abdomen even after the neutralizer was given and pain stopped, but the pain itself had no definite relation to the peristalsis at any time during the tracing.

It has always been difficult to explain the quick, unfailing relief to the pain of peptic ulcer obtained by giving a sufficient quantity of neutralizer, by emptying the stomach or by eating on the basis of motor activity alone. It would seem that a similar quick change in motor

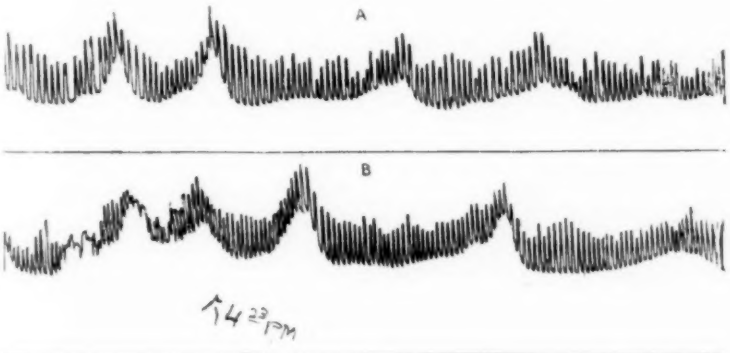

Fig. 7.—*A*, peristalsis before alkali administration; *B*, after alkali administration; no pain throughout.

phenomena should be demonstrable. It also is difficult to conceive how soda bicarbonate, calcium carbonate or calcined magnesia could depress localized spasm so completely and quickly, without affecting general motor activity as well, though it is conceivable that they might in this way relieve ulcer pain, if local spasm were the cause.

CONCLUSIONS

In this series of experiments there is no evidence that soda bicarbonate and calcium carbonate relieve the pain of ulcer through lowering tension or tone or through decreasing peristalsis of the stomach, so far as either of these factors can be recorded by the method used.

The fact that, in ten of the twenty-three tracings, varying increases of peristalsis were recorded, and in four, only decreases following the neutralizer is not of sufficient significance in so small a number of tracings as to rule out the factor of the possible coincidence of peristaltic

changes that may occur in the progress of digestion in ulcer patients. If one attached significance to the increase in peristalsis following alkali shown in ten, one would again need to explain the absence of any change in nearly as great a number (nine).

Carlson has shown that peristaltic activity of the stomach is present when food and secretion are in the stomach, but that it is most active in the fasting stomach. Dr. Sippy showed, in innumerable hospital tests, that the pain of uncomplicated ulcer is present only when gastric content in adequate quantity and quality is present in the stomach. In the opinion of the writer, the pain and the peristalsis are probably coincidental.

The foregoing experiments do not bear out the theory that the peristalsis causes the pain. There probably are a number of responsible factors, none of them as yet definitely proved or known.

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NONSPECIFIC ULCERATIVE COLITIS *

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NEW YORK

Introduction and definition of terms.
Gross and microscopic anatomy of the colon.
Physiology of the colon.
Clinical aspects of nonspecific ulcerative colitis.
  Incidence.
  Age.
  Sex.
  Mortality.
  Residence.
  Family history.
  Occupation.
  Previous illness.
  Mode of onset.
  Duration of symptoms.
  Clinical picture.
Analysis of special symptoms and signs.
  Diarrhea.
  Character of stools.
  Abdominal pain.
  Abdominal tenderness.
  Incontinence.
  Vomiting.
  Loss in weight.
  Fever.
  Sigmoidoscopic examination.
  Blood changes.
  Miscellaneous laboratory data.
Duration and course of nonspecific ulcerative colitis.
Prognosis.
Cause of death.
Operative findings.
Bacteriology of nonspecific ulcerative colitis.
Pathology of nonspecific ulcerative colitis.
Theories as to the etiology of nonspecific ulcerative colitis.
Treatment.
Conclusions.

INTRODUCTION AND DEFINITION OF TERMS

The subject of ulcerative colitis of unknown etiology has received comparatively little attention since the condition was first described by Wilks [1] and White.[2] Its prevalence and rapid spread in asylums in

* These investigations were made possible through the liberality of Mr. W. D. Thornton in establishing the Thornton Research Fund. All the cases described are taken from the service of Dr. Jerome M. Lynch at St. Bartholomew's Hospital.

1. Wilks, S., and Moxon, W.: Lectures on Pathological Anatomy, Ed. 2, 1875, p. 408.

2. White, W. H.: On Simple Ulcerative Colitis and Other Rare Intestinal Ulcers, Guy's Hosp. Rep. **45**:131, 1888.

England at that time, particularly in those for the insane, was made the subject of investigation by a special medical commission. In a review of these accounts, one cannot help thinking that many cases of asylum dysentery described in the early English reports were really bacillary or amebic dysentery.[3] In 1902, Vedder and Duval[4] proved that epidemics of dysentery occurring in American institutions were caused by *Bacillus dysenteriae*. Moreover, in 1904, Eyre[5] proved that the epidemics occurring in English institutions were caused by *Bacillus dysenteriae*. Between the years 1901 and 1904, 1,155 cases occurred in the London county asylums, 266 of them being fatal. Yet in spite of stringent attempts at isolation and disinfection, there was no diminution in the incidence of the disease.[6] The difficulty of isolating *Bacillus dysenteriae*, except at the onset of acute cases of bacillary dysentery, because of the rapidity with which this organism is outnumbered by *Bacillus coli*, makes it seem quite likely that a great many cases of ulcerative colitis might commence as a specific infection but rapidly pass over to a nonspecific type. Knobel, Ackland, Targett[7] and others suggested that the condition might be a trophic neurosis associated with disease of the nervous system. The strong resemblance of symptoms and lesions with absence of any etiologic factors, in the English cases, lead us to conclude that the majority, if not all, of them could be classified under nonspecific ulcerative colitis. The distinct separation of this type from bacillary dysentery was recognized by such eminent observers as Osler and Allchin.

The terms "asylum dysentery," "idiopathic ulcerative colitis," "innominate ulcerative colitis," "simple ulcerative colitis" and "ulcerative colitis" have been used to describe what is apparently one and the same condition. Because of the lack of evidence pointing to the presence of a definite etiologic factor, Lynch has applied the name of "nonspecific ulcerative colitis" to this group of cases. Our acceptance of this title will, of necessity, bar consideration of ulcerative conditions of the colon having any of the following etiologic bases:

1. Constitutional disease—Bright's disease, gout, pneumonia, lead poisoning and cardiac disease.

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3. Gemmel, J. F.: Idiopathic Ulcerative Colitis, 1898.

4. Vedder, E. B., and Duval, C. W.: The Etiology of Acute Dysentery in the United States, J. Exper. Med. **6**:181-205, 1902.

5. Eyre, J. W. H.: Asylum Dysentery in Relation to B. Dysenteriae, Brit. M. J. **1**:1002-1004, 1904.

6. White, W. H., cited by Albutt and Rolleston: System of Medicine (Diseases of the Colon) **3**:826-840, 1907.

7. Quoted from Tuttle, J. P.: Diseases of the Anus, Rectum and Pelvic Colon, 1906, pp. 180-183.

2. Specific bacterial or protozoal ulcerative conditions—typhoid, ameba histolytica dysentery, bacillary dysentery, tuberculosis and syphilis.

3. Malignant disease.

4. Trophic disturbances due to interference in the nerve supply of the colon.

5. Mechanical trauma—hard feces and foreign bodies.

6. Vascular changes—embolism of the superior mesenteric artery and cirrhosis of the liver.

GROSS AND MICROSCOPIC ANATOMY OF THE COLON

Gross Anatomy.—In man, the colon starts in the right iliac region as a dilated pouch, the cecum, into which the small intestine opens, passing the ileocecal valve. From the cecum, the colon passes up toward the liver, then transversely across the upper part of the abdominal cavity to the spleen and finally downward to join the rectum at the rectosigmoidal sphincter. The average length of the colon is 22 inches (55.5 cm.). The cecum and ascending colon are usually only partly covered by peritoneum, while the remainder of the colon possesses a mesentery. The sigmoid flexure or pelvic colon is the narrowest portion of the colon and is mobile by reason of its long mesentery. Commencing at the base of the appendix and surrounding it is a layer of longitudinal muscular fibers which, as it passes upward on the colon, forms three flat longitudinal bands, each being about 12 mm. in width. These bands are about one-sixth shorter than the intestine proper and thus cause sacculation of the colon. The mucous membrane of the colon is smooth and raised into folds corresponding to the spaces between the sacculi.

The arterial supply of the colon is derived from the superior and inferior mesenteric branches of the descending aorta, the former supplying the cecum, ascending and right part of the transverse colon, the latter supplying the remainder of the transverse and all of the descending colon, sigmoid flexure and part of the rectum. The arterial branches in the wall of the colon do not freely anastomose. Free anastomoses usually occur by a series of loops which lie close to the mesenteric borders of the colon. In the sigmoid flexure, the anastomoses usually occur nearer the base of the mesocolon. The superior mesenteric vein follows the general course of the artery and unites with the splenic vein behind the neck of the pancreas to form the portal vein. The inferior mesenteric vein begins as the superior hemorrhoidal of the rectum and usually empties into the splenic vein.

The lymphatic supply of the colon follows the course of the blood vessels. According to Jamieson and Dobson,[8] the lymph nodes can be divided into the following groups:

1. The epiploic nodes, which lie on the intestinal wall and in the appendixes epiploicae, being especially numerous in the pelvic colon. These drain into Groups 2 and 3.

2. The paracolic nodes, which lie along the mesenteric border of the colon.

3. The intermediate groups, which lie along the arteries.

4. The main groups: middle colic, lying on the middle colic artery, and left colic, lying on the left colic artery near its origin and on the terminal portion of the mesenteric vein. These nodes drain into the superior mesenteric, celiac and lumbar nodes. The inferior mesenteric group lies on the artery and drains into the lumbar glands which drain the pelvic colon.

Some of the lymphatics of the left portion of the transverse colon drain into the nodes at the hilum of the spleen through the gastrocolic omentum.

The nerve supply to the colon is derived from the sympathetic plexuses around the branches of the superior and inferior mesenteric arteries.

Microscopic Anatomy.—The colon consists of four coats:

1. Mucosa, made up of a simple columnar epithelium with goblet cells resting on a basement membrane, beneath which is the tunica propria containing capillaries and diffuse lymphoid tissue. Externally is the muscularis mucosae. The glands are of the simple tubular type.

2. Submucosa, containing solitary follicles.

3. Muscularis, consisting of an internal circular layer (especially thick in the intervals between the sacculi and forming the internal sphincter of the anus) and an outer longitudinal layer forming the bands, or taeniae, above described.

4. Serosa, derived from peritoneum, covering the sigmoid and cecum completely, the ascending and descending colon in front and at the sides and the transverse colon almost completely.

PHYSIOLOGY OF THE COLON

Hertz[9] finds that, in man, it requires about two hours for food to pass from the ileocecal valve to the hepatic flexure, and about four and

8. Quoted from Mummery, P. L.: Diseases of the Colon, 1910, pp. 7-8.

9. Hertz, A. H.: The Passage of Food Along the Human Alimentary Canal, Guy's Hosp. Rep. **61**:389-427, 1907.

a half hours to reach the splenic flexure. From this point, the food material advances very slowly toward the rectum. It requires from sixteen to seventeen hours for food to pass from the splenic flexure to the lower end of the sigmoid, and six hours to pass through the sigmoid, as compared with four and three-eighths hours for movement through the 20 feet (50 cm.) of small intestine. Cannon [10] divides the large intestine into two parts: In the first corresponding to the cecum, ascending and transverse colon, the most frequent movement is antiperistalsis. The fluid or semifluid material is forced back toward the small intestine, the entrance to which, however, is guarded by the ileocecal valve. The object of this delay is primarily for the absorption of

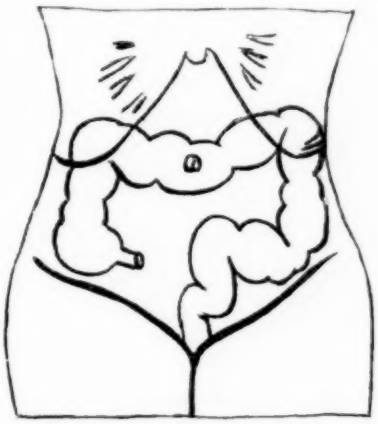

Fig. 1.—Projection of outline of colon on abdominal parietes

water and secondarily to complete the process of digestion. The importance of fluid absorption is evident from the phenomenon of intense thirst displayed by patients having a right inguinal colotomy. According to Keith and Mummery, the cecum bears the same relationship to the large intestine as the stomach bears to the small intestine. In some of the lower animals, the cecum is actually the main organ of digestion. In the second portion—the descending colon—the food material, which is now quite solid, is moved on by peristaltic waves toward the rectum.

The motor nerve fibers leave the cord in the second to fourth sacral nerves, and reach the colon through the hypogastric plexus. The inhibitory fibers probably leave the cord in the lumbar nerves and reach the colon through the sympathetic chain and inferior mesenteric ganglions. The type of movement in the colon is generally held to be

10. Cannon, W. B.: The Movements of the Intestines Studied by Means of the Roentgen Rays, Am. J. Physiol. **6**:251, 1902.

the same as in the small intestine, except for the relative infrequency in the former: a local rhythmical constriction and a progressive peristaltic movement. According to Hertz,[9] fecal material is normally absent from the rectum except just before defecation. The sigmoid flexure acts as the normal fecal reservoir. The feces are retained in the rectum by the tonicity of the internal and external sphincters, the latter being in greater tone than the former. With distention of the rectum by the feces, there arises the normal stimulus to defecate, which act is effected by peristaltic action of the colon and rectum, occurring simultaneously with relaxation of the sphincters and fixation of the diaphragm.

It is interesting to note that the normal mucous membrane of the colon does not possess ordinary tactile or pain sensation. The latter is

TABLE 1.—*Comparative Figures of Frequency of Nonspecific Ulcerative Colitis*

Hospital	Period	Years	Number of Cases
St. Bartholomew's Hospital, New York City...	1920-1923	approximately, 3	41
Guy's Hospital, England.....	1888-1907	20	50
London Hospital, England.....	1894-1908	15	22*
Royal Free Hospital, England.....	1883-1907	25	2
St. Bartholomew's Hospital, England.....	.....	..	24
St. George's Hospital, England.....	1883-1906	23	19
St. Mary's Hospital, England.....	1884-1907	23	19
St. Thomas' Hospital, England.....	1883-1908	25½	80
University College Hospital, England.....	1883-1908	25	38
Westminster Hospital, England.....	1884-1908	25	42

* Based on postmortem reports.

also absent from the visceral peritoneum. The parietal peritoneum and the mesentery of the colon, however, do possess pain sensation. The mucous membranes of the lower part of the rectum also possess definite pain sensation. Violent peristalsis will also produce pain due to muscular contraction of the intestine.

CLINICAL ASPECTS OF NONSPECIFIC ULCERATIVE COLITIS

Incidence.—During the period of thirty-four months (December, 1920, to October, 1923), our records show a total number of forty-one cases of nonspecific ulcerative colitis (combining the private records of Dr. Jerome M. Lynch and those of St. Bartholomew's Hospital).

Table 1 gives a comparison of our figures with those of other institutions. As stated above, the English figures probably include some cases of bacillary dysentery, but, because of the incomplete or doubtful bacteriologic data, they could not be excluded.

The relatively greater frequency shown by our figures is probably due not to any increase in the incidence of nonspecific ulcerative colitis, but, rather, to greater care in recognition of the disease.

Age.—The age at the time of onset of symptoms, in our series, is shown in Table 2.

Analysis of the figures in Table 2 shows the greatest incidence (70 per cent.) between the ages of 20 and 40 years, as summarized in Table 3.

Our figures correspond to those reported by other institutions, e. g., Guy's Hospital, average age, 35.8; London Hospital, 37; St. Bartholomew's Hospital, 39.2; St. Thomas' Hospital, 70 per cent. between 20 and 45 years; University College Hospital, forty out of fifty-one patients

TABLE 2.—*Age Incidence of Nonspecific Ulcerative Colitis in Forty-One Cases*

Case Number	Age, Years	Case Number	Age, Years
1	31	22	15
2	29	23	25
3	24	24	34
4	40	25	45
5	30	26	27
6	61	27	17
7	27	28	35
8	36	29	52
9	33	30	21 months
10	29	31	36
11	36	32	50
12	23	33	43
13	30	34	29
14	32	35	24
15	34	36	50
16	18	37	28
17	29	38	60
18	32	39	41
19	35	40	23
20	43	41	34
21	22		

TABLE 3.—*Summary of Age Incidence*

Age	Number of Cases
Less than 20 years	4
From 20 to 30 years	16
From 30 to 40 years	12
From 40 to 50 years	6
Over 50 years	3

between 20 and 40 years; Westminster Hospital, thirty-one out of forty-two patients between 20 and 40 years.

Sex.—In our series, sex incidence was as follows: male, nineteen; female, twenty-two, the single women numbering eight and the married fourteen.

It will be seen that both sexes were affected about equally, and married women more than single women.

Mortality.—Five of our patients died: Patient 20 of pneumonia; Patient 22 of acute infection of the small intestine; Patient 27 of acute dilatation of the stomach following ileostomy; Patient 41 of perforation of the cecum with general peritonitis; Patient 8 of postoperative vol-

vulus of the small intestine. Of course, a short follow-up period of three years would not justify one in drawing any conclusions from these figures, especially because of the susceptibility of these patients to reinfection from time to time.

Residence.—We have been able to elicit no evidence pointing to an infection (bacterial or protozoal), endemic or epidemic. Almost all our patients came from localities in which hygienic conditions were good, and none traveled to any extent.

Family History.—No patient gave a history of similar disease in any other member of the family.

Occupation.—The great variety of occupations in which these patients were engaged makes this source of origin of the disease seem quite unlikely. Most of the patients had more or less sedentary occupations not requiring extensive contact with persons or with poisonous materials.

TABLE 4.—*Incidence of Previous Illness Having Possible Etiologic Relationship*

Associated with, or possibly following operation for fistula (Cases 5 and 35)	2
Indiscretion in diet, especially sugar or milk (Case 6)	1
Constipation (Cases 11, 19, 1 and 4)	4
Nervous shock (Case 12)	1
Following operation for hemorrhoids (Cases 13 and 14)	2
Following operation for appendicitis (Case 17)	1
Following operation for ovarian tumor (Case 9)	1
Following attack of acute colitis (Case 20)	1
Associated with ulcerative condition of mouth and purulent eruptions on skin (Case 27)	1
Hyperthyroidism (Case 33)	1
Influenza (Case 34)	1
Associated with attacks of indigestion (Cases 38 and 39)	2

In the remaining twenty-three cases, the patients could not definitely associate the onset of the disease with any other condition. They were apparently quite well. It is interesting to note that six of the eighteen cases in Table 4 followed operations, and four of these were on the rectum. "Indiscretion in diet" (Case 6) might be included under "attacks of indigestion" (Cases 38 and 39) possibly causing ulcerative colitis through the local irritating action of ingested food or in the process of elimination of metabolic food poisons through the wall of the colon. Severe constipation is undoubtedly a factor, in that hard fecal masses may mechanically injure the wall of the colon. The nervous influences at play in hyperthyroidism and "nervous shock" may possibly exert their effects by means of the excessive peristalsis and diarrhea often associated with these conditions. Case 27 is very interesting in that this patient seemed to have a susceptibility to ulcerative conditions all over the body. He eventually died with involvement of the small intestine. This patient corresponds to the type described by

Tuttle as the anemic, broken down person suffering from some other form of disease or exhausting condition.

Mummery [11] cites a case of nonspecific colitis which started as an acute specific dysentery. The protozoal agent, however, soon disappeared, and only *Bacillus coli* or streptococci could be demonstrated as possible etiologic agents. Similar observations have been made by Lynch.[12]

Yeomans [13] describes a series of sixty-five cases, thirty-seven of which had no etiologic basis. Of the remainder, five gave a history of amebiasis, six of dietary indiscretion, five of severe constipation and three of exposure.

TABLE 5.—*Duration of Symptoms in Thirty-Five Cases Before Coming Under Observation*

Case	Duration	Case	Duration
1	5 years	20	1 year
2	9 years	22	2 years
3	2 years	23	2 years
4	2 weeks	25	5 weeks
5	4 years	26	1 year
6	15 years	27	2 years
7	8 months	28	1 month
8	14 months	29	2 years
9	20 years	30	8 months
10	2½ years	31	6 months
11	2 years	33	18 months
12	10 months	34	18 months
14	10 years	35	4 years
15	3 weeks	38	18 months
16	9 months	39	10 years
17	2 years	40	1 year
18	1 year	41	5 weeks
19	4 years		

Mode of Onset.—Of those cases giving a definite time of onset, twenty-one were gradual and seventeen acute. The first symptoms or signs noticed by the patients were as follows: bloody stool in seven cases; diarrhea and bloody stool in seven cases; abdominal pain, six cases; abdominal pain and diarrhea, four; abdominal pain and bloody stool, three; mucus and blood in stool, three; pus and blood in stool, two; diarrhea, two, and constipation alternating with diarrhea in one case.

It will be noted that most of the cases were of rather long duration, indicating that the infection, if present at all, must have been subacute. In fact, the cases which came under our observation early were all severe.

11. Mummery, P. L.: The Operative Treatment of Ulcerative Colitis, Brit. M. J. **1**:497 (April 10) 1920.

12. Lynch, J. M.: Diseases of the Rectum and Colon, 1914, p. 334.

13. Yeomans, F. C.: Chronic Ulcerative Colitis, J. A. M. A. **77**:2043 (Dec. 24) 1921.

Clinical Picture.—The acute cases often begin with severe diarrhea and colicky or griping pain, usually referred to the front of the abdomen. As a rule, however, the onset is gradual, with passage of blood and mucus in the stool. The abdominal pain, if severe at first, may entirely disappear in a short time, only to recur after a period varying from several minutes to hours. Relief is usually obtained by movement of the bowels, especially if accompanied by passage of flatus. Tenesmus may be present if the rectum is involved. The passage of blood, mucus and pus by rectum is characteristic of ulcerative colitis. According to Hurst,[14] when the pelvic colon and rectum alone are involved, the stools may be solid. In other cases, diarrhea alternates with constipation. Often a patient will complain of frequency and urgency, but does not feel satisfied at stool. There still remains a more or less constant desire to defecate. In many cases, vomiting is a troublesome symptom; in others, frequency of micturition is evident. The constant loss of blood, accompanied by passage of great quantities of water and undigested food in the diarrheal stools, soon leads to loss in weight, anemia, anorexia and marked weakness. In many cases, the patient is bedridden, sallow in appearance and often desperately ill. There is an accompanying hyperpyrexia, usually not very high, varying around 100-102 F., by rectum, except when a complication exists. Death usually occurs from exhaustion.

The foregoing description applies to an average fairly acute case. All sorts of variations occur. Some of our patients, while under observation in the hospital, ran no fever at all. Some have only two or three bowel movements a day. Loss of weight is a very constant feature, one patient (Case 18) losing 35 pounds (15.9 kg.) within one year. In many patients, one may feel what is often described as a "thickening" of the cecum and sigmoid, probably due to a hypertonic state of the muscular coat. Pressure on the sigmoid will often produce a desire to defecate.

ANALYSIS OF SPECIAL SYMPTOMS AND SIGNS

Diarrhea.—This symptom, while usually occurring early, ensues quite regularly sooner or later in all cases showing ulcerating lesions anywhere above the rectum. It is probably due to excessive peristalsis, which is, in turn, brought about by the irritating effect of intestinal contents on the exposed nerves of open ulcers. Mummery found that a traumatic stimulus to the intestinal mucosa, such as nipping it with the end of a pair of forceps, always resulted in a marked peristaltic contraction, which was always local. The diarrhea may vary from a

14. Hurst, A. F.: Ulcerative Colitis, Guy's Hosp. Rep. **71**:26 (Jan.) 1921.

few stools each day to twenty or more. The largest number of stools are passed usually in the morning, and the first movement may be almost solid. One or more bowel movements occur after each meal. When the pelvic colon and rectum alone are involved, the stools may be solid. In a number of our cases, constipation alternating with diarrhea was the rule (Cases 28 and 30). Sometimes there is a long history of slight bowel irregularity, with occasional passage of mucus and blood. One patient (Case 35) was constipated throughout his illness.

Character of Stools.—The stools are most often fluid, dark brown and foul. When accompanied with blood, the latter is usually also fluid and bright red, indicating its recent origin. Some patients note the presence of blood, especially after a period of constipation. We have often noted that the bloody stool may occur independently of the diarrheal condition. The blood is not thoroughly mixed with the stool, and, when the latter contains much fluid and only some fecal material, the solid particles may be specked with blood. Occasionally, small or large recently detached clots may be passed. The mucus may be clear or turbid from admixture of pus. Hale White describes the occasional presence of shreddy sloughs, which, under the microscope, appear to be quite structureless and show an occasional epithelial cell or leukocyte.

Examination of the feces shows that the food material has been fairly well digested, except in cases in which the ileum is involved. Here much undigested starch and proteid (meat fibers) are present; the stools are offensive, and a great deal of flatus is passed.[15] The feces are usually alkaline in reaction except when a great deal of carbohydrate fermentation has occurred.

Abdominal Pain.—Most of our patients complained of a colicky abdominal pain just before defecation or, rather, the pain was always accompanied by a desire to defecate. Movement of the bowels usually brought relief, especially if accompanied by the passage of flatus. One of our patients (Case 22) complained of frequent abdominal pain, without any desire to defecate. Occasionally, the symptoms are rather those of great frequency and urgency (Case 23). Tenesmus is present usually when the rectum is involved. In one of our very interesting cases (Case 25), the pain was more marked after stool, radiating up the back and down both thighs. After passage of blood and mucus, there was always a feeling of unfinished stool. Case 34 gave a history of blood and mucous diarrhea entirely unaccompanied by pain. In most patients, the attacks of abdominal pain are short lived, but recurrence is the rule.

15. Schmidt, A. I.: Klinik der Darmkrankheiten, 1921.

Abdominal Tenderness.—Only one patient (Case 41) in our series gave evidence of abdominal tenderness. Postmortem examination showed the presence of a perforation of the cecum close to the base of the appendix.

Incontinence.—Four cases (Cases 38, 41, 26 and 39) of the more severe type showed incontinence for long periods during their illness. The loss of sphincter control is often associated with severe debilitating chronic diarrheal conditions.

Vomiting.—In two cases (Cases 39 and 12), this symptom was a troublesome one. Vomiting is not a constant feature in nonspecific ulcerative colitis, and, if present, is probably due to the absorption of toxic material from the intestine.

Loss in Weight.—This is noted in practically every case, and often becomes a serious factor in the prognosis. Table 6 indicates the result of a survey of our series.

TABLE 6.—*Loss of Weight in Nine Cases*

Case	Loss in Pounds (Kilograms)	Period
3	11 (5)	8 months
6	20 (9)	6 years
8	10 (4.5)	1¼ years
9	19 (8.6)	1 year
15	25 (11.3)	5 months
18	35 (15.9)	1 year
20	50 (22.7)	7 years
26	35 (15.9)	1 year
33	17 (7.7)	1½ years

Two of our patients showed no loss in weight. The remainder, not included in Table 6, lost weight, but no fairly accurate estimate could be made. It should be remembered that many of these patients place themselves on a very restricted diet and this, in conjunction with loss through diarrheal stools, often leads to marked reduction in weight.

Fever.—Three of our patients (Cases 20, 21 and 33) experienced chills, either at the onset of the first attack or during recurrence. Most cases show a moderate rise in temperature, the average being somewhere between 100 and 101 F. Some cases show an absolutely normal temperature curve. Sharp rises will occur, however, with complications, such as perforation or intramural abscess. Figure 2 is illustrative of rises in temperature due to the formation of intramural abscesses.

In the average patient, the affection seems to run a rather subacute course with little or no hyperpyrexia. One patient (Case 15), who subsequently became entirely well, ran a temperature of 95 F. on two occasions.

Sigmoidoscopic Examination.—As only one of our cases came to necropsy, the following descriptions of individual cases may be of interest:

CASE 1.—The mucosa of the colon was very boggy and bled easily. The entire field was covered with purulent and bloody exudate. Above 8 cm., no bleeding was seen, but a whitish fluid was present.

CASE 3.—Scattered irregularly over the rectum and a large part of the sigmoid, sometimes in groups, elevated irregular papules with whitish necrotic tops were to be seen. The mucosa also showed some irregular, small, clean ulcers. There appeared to be an unusually small amount of inflammatory reaction present.

CASE 4.—The mucous membrane showed irregular ulcerations (denudation). There were also elevated granulation areas surrounded by depressions, in

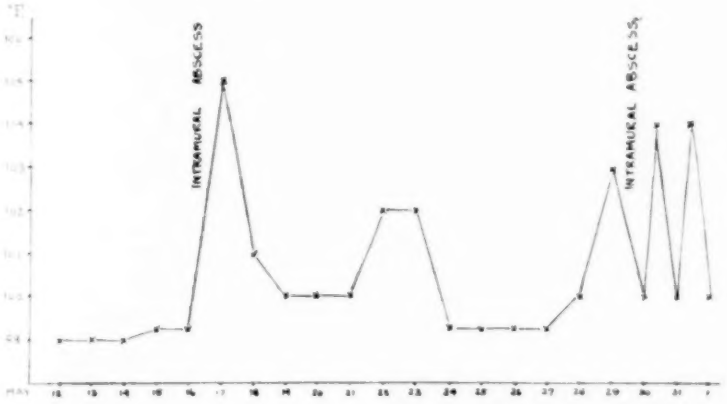

Fig. 2 (Case 16).—Temperature chart in case of intramural abscess. A similar condition occurred at the time of this patient's previous admission, when the temperature rose rather suddenly from 99 to 103 F., lasting twenty-four hours and coming down, by lysis, during a period of about a week.

which pus might be seen. The ulcers partially surrounded the bowel in several places.

CASE 5.—The internal sphincter muscle was almost destroyed (previous operative procedures). On digital examination, one could detect a "lumpiness" of the bowel, with intervals of smooth mucosa as far as the fingers could reach. On the left side, parallel with the 8 or 9 o'clock position of a clock hand, was a large inflammatory mass. The bowel was covered with mucus, pus and blood, principally in the inflamed region. The inflamed area seemed to follow the course of the blood vessels on the outside. There were some linear, serpiginous inflamed areas. Here and there, one saw prominent longitudinal masses, about the size and shape of the first phalanx of the index finger, composed of pinkish granulation tissue which was almost cartilaginous to the touch.

CASE 7.—The mucosa was very red and angry looking, and was covered with great quantities of mucus. There were a few scattered ulcerated areas to be seen. The entire mucosa bled very easily.

CASE 10.—The mucosa was edematous and vesicular and oozed a serosanguineous fluid. It bled easily, and was covered irregularly by a flocculent, grayish white membrane. On the edge of the valve was seen a definite shallow ulcer. Grayish white spots floated on top of the serous exudate, giving the mucosa a speckled appearance.

CASE 16.—Many small ulcers were present, extending from the sigmoid to the anal margin. Some of these ulcers were covered with whitish membrane, but the majority were filled with granulation tissue. When membrane is present, it is stained with blood and, on removal, leaves a raw, denuded surface.

CASE 18.—Segmental infection was present, beginning at a point 9 cm. from the anus and extending up to 30 cm. The rectal area showed evidence of previous infection. There were denuded ulcerated areas extending from a point about 12 cm. from the anus to the apex of the sigmoid, and probably much higher. In the rectum, these ulcers circumvented the wall. A large amount of reddish, thick fluid was present (blood and detritus). At about 10 cm., there was a partial stenosis through which exuded an admixture of pus and blood.

CASE 21.—The mucosa of the colon was extremely red, of granular appearance, and covered with pus, mucus and blood. This condition existed as far as one could reach with the sigmoidoscope, and probably extended as far as the cecum.

CASE 24.—The rectal and sigmoidal mucosa appeared to be acutely inflamed. An occasional ulcer might be seen. At a point just above the internal sphincter on the left side, there was an ulcerated area 4 cm. in length. The entire inflamed region was covered with pus and blood. All the ulcers were necrotic and irregular.

CASE 31.—In this case, almost all the lesions were confined to the rectum. Here, the mucosa appeared red, boggy and edematous. The slightest pressure caused pain. Numerous long, sharply defined ulcers were present. In some places, the mucosa was covered by a whitish membrane which resembled macerated skin. Most of the ulcers were on the anterior surface of the rectum, which was covered by a large quantity of pus and blood.

CASE 33.—The colon was covered by a thick exudate. Epithelial cell masses floating on the top of this fluid gave the bowel a bosselated appearance. On removing the exudate, the wall presented a granular appearance. The mucosa bled easily.

CASE 36.—The mucosa was very edematous. Clusters of papules were irregularly distributed from the anus to the sigmoid. These could be seen in their various phases, beginning with papules and going on to vesicles, papules with necrotic tops and papules with regular craters having a smooth round wall, sloping symmetrically toward the center. In places, the lesions had reached the ulcerative stage, especially on the edge of the first valve. Here, the ulcerative process was irregular and had a tendency to extend circumferentially rather than longitudinally. The whole area was covered by mucus, pus and serum.

CASE 38.—Ulcers were seen scattered here and there, interspersed with polyps, varying in size from 1 to 20 mm. There was also seen one granular, confluent ulcer covered with exudate, which consisted of blood, mucus and pus. At a point 7 cm. from the anus, there was a stricture 6 cm. in length.

The foregoing cases have been chosen as illustrating the variety of lesions one may expect to see in the course of sigmoidoscopic examination.

Blood Changes.—Most cases present a secondary anemia of moderate severity. Cases have been reported, however, in which the anemia has

been so severe as to resemble pernicious anemia. Three of our patients (Cases 20, 30 and 34) showed a marked anemia, and two of these (Cases 20 and 30) subsequently died of pneumonia. The figures for these two fatal cases were as follows: Case 20, hemoglobin, 38 per cent., and erythrocytes, 2,300,000 per cubic millimeter; Case 30, hemoglobin, 35 per cent., and erythrocytes, 2,160,000 per cubic millimeter.

Miscellaneous Laboratory Data.—In only one case (Case 31 was there any history or laboratory evidence of syphilitic infection. Dec. 7, 1912, the blood and spinal fluid gave a positive Wassermann reaction. The spinal fluid showed a cytology of 181 cells per cubic millimeter, and globulin was present. April 14, 1914, after intensive arsphenamin therapy, the blood and spinal fluid examinations proved entirely negative. Spinal fluid cytology was 4 cells per cubic millimeter, and globulin was

Fig. 3.—Sigmoidoscopic picture in idiopathic ulcerative colitis; absence of granular appearance of mucosa.

absent. The onset of illness occurred one year later, and all examinations seemed to point to the nonspecific nature of the colon infection.

Most of our cases showed some albumin and occasional casts in the urine at some time during the period of observation. Blood chemical studies, gastric analysis and basal metabolism determinations proved to be negative.

Roentgen-ray examinations may show absence of normal haustration, mottling of the wall due to ulceration and abnormal narrowing of the intestine due to spasm.

DURATION AND COURSE OF NONSPECIFIC ULCERATIVE COLITIS

If one disregards the duration of acute attacks and bases his estimate entirely on sigmoidoscopic or operative findings, he will be impressed by the great variations in the duration and course of this infection. Much depends on the type of treatment instituted. Patients left to heal spon-

taneously without medical or surgical intervention almost invariably fare badly. Others on whom the proper treatment has been instituted may clear up in a few weeks or go on for years with periodic acute exacerbations. Some do not get along no matter what procedure is followed, and this applies especially to cases which have come under observation late in the disease, when the infection has already spread to the small intestine. Undoubtedly, the factor of individual resistance to disease plays a great part in the healing process in ulcerative colitis. The poorly nourished, weakly, sallow patient almost always has a hard struggle to overcome this condition. Recurrence and chronicity are typical of nonspecific ulcerative colitis. Yeomans [13] reports an average duration of two months. In our series, the average period of duration was ten months if reckoned from the date the patients first came under our observation and treatment until complete healing occurred, as evidenced by the sigmoidoscopic examination and disappearance of symptoms.

TABLE 7.—*Duration of Disease from Time Treatment Was Instituted Until Apparent Cure*

Case	Duration	Permanence to Date
1	1 month	1½ years
2	3 months	7⅔ years
3*	2 months	1½ years
7	1 month	1 month
9	2 years	4½ years
11	4 months	3½ years
21	2 years	5 years
31*	2 months	5 years
35	2¼ years	8 years
40	1 year	1 year

* Subsequent recurrence with recovery.

Sixteen patients were discharged improved, but not entirely healed. Nearly all of these, for some reason or other, could not remain in the hospital long enough to complete treatment. Nine patients left the hospital unrelieved after a short stay (incomplete treatment), and have not been accounted for since discharge. Five patients remained unrelieved and subsequently died.

The clinical course of the disease, aside from the features above described, depends almost entirely on the local pathologic condition. If the lesions are progressive, intramural abscesses of the colon may form (Fig. 2). Further extension will involve the peritoneum or neighboring viscera.

PROGNOSIS

From our experience with this condition, we are inclined to make a rather guarded prognosis as to permanence of cure. The brilliant results obtained by colonic irrigations tend to make one overenthusiastic. The ten cases showing complete healing have remained apparently

entirely well for periods varying from one to eight years (except a recent one, Case 7, which has been followed up for only one month). As shown in necropsy reports, there is a tendency for the ulcerative lesions to heal spontaneously so that there is a possibility that in mild cases, the patients never seek medical attention. In any case, one should advise the patient of the long, painstaking course of treatment, though one may be occasionally agreeably surprised at the rapidity of healing in even the most chronic cases.

CAUSES OF DEATH

The causes of death in our cases were as follows: in Case 8, volvulus of the small intestine; Case 20, pneumonia; Case 22, extension of infection to the small intestine; Case 27, postoperative (ileostomy) dilatation of the stomach; Case 41, perforation of the cecum, and Case 30, pneumonia.

Fig. 4.—Sigmoidoscopic picture in idiopathic ulcerative colitis; granular appearance of mucosa.

OPERATIVE FINDINGS

Case 3.—Ileostomy was done. The sigmoid and lower 6 inches (15.2 cm.) of the ileum was much thickened.

Case 27.—Ileostomy was done. The colon was enormously thickened. Fifteen inches (37.5 cm.) of the small intestine was involved.

Case 21.—Removal of cecum was done. The mucosa was acutely inflamed and hemorrhagic. The entire wall of the cecum was edematous.

BACTERIOLOGY OF NONSPECIFIC ULCERATIVE COLITIS

A review of the bacteriology of nonspecific ulcerative colitis is a study of the bacteriology of the colon. Our knowledge as regards the latter is very limited,[15] as there are any number of organisms in the feces which have not yet been identified or definitely classified. This is especially true of the gram-positive bacillus group. It has been observed

by Kendall [16] and others that changes in the intestinal flora depend somewhat on the diet of the person. It is interesting to note the heterogeneous variety of intestinal bacteria in the adult on the usual mixed diet as compared with the homogeneity of types found in the nursing infant. Under normal conditions in the adult, *Bacillus coli* comprises about 75 per cent. of the viable bacteria of the feces. The cecum and the ascending colon are the regions of most intense bacterial growth in health, but the number of living bacteria diminish abruptly from the sigmoid to the rectum, where the feces are fairly well desiccated.

The stomach, in health, is practically free from bacteria. Studies by Kendall have shown that the most common bacteria in the duodenum are the enterococcus and members of the mucosus capsulatus group. As we advance down the small intestine the cocci still predominate as far as the upper ileum, but a moderate number of organisms of the colon group begin to appear. In the ileocecal region, the flora is usually represented by the aerogenic bacilli of the colon type and spore bearers of the mesenteric group. In the colon, we obtain facultative-fermentative bacteria: the colon-proteus group, various aerobic liquifying bacilli (both spore bearing and nonspore bearing) and some anaerobic bacteria. The change in bacterial flora, as we advance down the intestinal tract, may be of prime importance in explaining the limitation of the lesions to the colon. This phenomenon may also account for the comparative immunity of the normal adult to intestinal infection. To quote Kendall: [16]

> It is probable that the significance of the intestinal flora lies rather in its potential antagonism to alien bacteria, which certainly gain entrance to the alimentary canal from time to time, than in any specific participation in the normal digestive process of the host. The normal intestinal flora may be regarded as intestinal parasites, just as the various bacteria which occur commonly on the skin are regarded as cutaneous parasites. It is important to realize that the normal intestinal organisms, like the cutaneous organisms, are opportunists, potentially capable of becoming invasive whenever the barriers which ordinarily suffice to limit their development to the lumen of the alimentary canal become impaired, giving rise to endogenous infection.

It was shown by Levin, who investigated the bacteriology of intestinal contents of Arctic animals at Spitzbergen, that, in most instances, the digestive tracts were entirely sterile. Thus, it seems quite certain that intestinal bacteria are not essential to life. If we assume (and our assumption may be incorrect) that the normal dominating organism in the colon (*Bacillus coli*) plays the part of a protector against dangerous foreign invaders, then it is logical to suppose that we must look elsewhere than for *Bacillus coli* as the etiologic pathogenic agent in ulcera-

16. Kendall, A. I.: Bacteriology, 1921.

tive colitis. Thus, Herter quotes a case of colitis in which *Bacillus coli* had been replaced by another organism as the dominant type. Recovery ensued when *Bacillus coli* had been again restored. Unfortunately, in our studies, we have failed to discover any displacement of *Bacillus coli* from its normal rôle. In general, most bacteriologic studies in nonspecific ulcerative colitis have been very unsatisfactory. Table 8 gives the results of bacteriologic investigation in eleven of our cases.

PATHOLOGY OF NONSPECIFIC ULCERATIVE COLITIS

Gross Pathology.—The pathologic process probably starts as an acute inflammation of the mucosa of the colon. This is followed by small patches of localized necrosis and sloughing off of the dead mucosa,

Fig. 5.—Sigmoidoscopic picture in idiopathic ulcerative colitis, showing tendency of such ulcers to become confluent. Such ulcers may even circumscribe the intestinal wall, leaving only small islands of intact mucosa; pus, mucus or blood may cover the surface.

leaving an ulcerated area which usually has the submucosa as a base. Recent ulcers are fairly clean cut; the edges are not undermined and vary in size, from a few millimeters to extending transversely around the colon. The tendency is to remain superficial and often adjacent ulcers coalesce, forming irregular, mapped out areas, with portions of intact mucosa between them. Often the intact mucosa appears to be undermined by the spreading ulcers, and, becoming edematous, gives the appearance of polyp formation. Hewitt and Howard [17] believe that, as healing begins, the margins of intact portions of mucosa are smoothed off, and the polypoid projections result. Often at a later period orifices of secreting tubules in the mucosa become blocked off by contraction of

17. Hewitt, J. H., and Howard, W. T.: Chronic Ulcerative Colitis with Polyps; a Consideration of the So-Called Colitis Polyposa (Virchow), Arch. Int. Med. **15**:714 (May) 1915.

scar tissue resulting in small retention cysts. This corresponds to the "colitis polyposa cystica" of Virchow. In the process of healing, new mucosa forms, and very little scarring results. Sigmoidoscopic examination may reveal only a few puckered areas or pigmented spots in the mucosa. In the more severe cases, the muscularis may form the floor of the ulcer and the peritoneum over this area may be reddened. Perforation may occur with local or generalized peritonitis. Multiple perforations are rare. In one of our cases, the cecum was involved, and the subsequent infection and necrosis resulted in a sudden extrusion of fecal material into the abdominal cavity. Some authors have described cases in which the colon wall was softened to such a degree that the palpating finger tore through it. It should be remembered that, in the

TABLE 8.—*Bacteriologic Studies in Nonspecific Ulcerative Colitis*

Case 3.—Feces: Gram-positive bacilli, 5 per cent.; gram-negative bacilli, 55 per cent.; gram-positive cocci, 40 per cent.
Case 7.—Purulent material from ulcerated area on colon: Heavy growth of coliform bacilli practically crowding out the usual gram-positive bacteria. No streptococci or staphylococci found. No Bacillus dysenteriae present
Case 10.—Feces: Bacillus coli-communis obtained in pure culture
Case 15.—Feces: Bacillus coli-communis predominate in culture
Case 16.—Feces: Bacillus coli-communis predominate. There are also two or three gram positive organisms present, one of them a spore bearer
Case 21.—Pus from cecum removed at operation: Bacillus coli-communis predominate. Unidentified short, slender bacillus and a large diplococcus are also present
Case 25.—Feces: Gram-negative bacteria, 15 per cent.; gram-positive bacteria, 85 per cent
Case 42.—Pus from rectum: Diphtheroid organisms associated with Bacillus coli-communis. No phagocyted bacteria are seen, which suggests that the significant organism may be Bacillus coli-communis
Case 30.—Feces: Gram-negative micrococcus, unidentified (this patient was a baby 21 months old)
Case 32.—Feces: Bacillus coli-communis and staphylococci predominate
Case 37.—Intestinal exudate: Bacillus proteus, Bacillus mucosus-capsulatus, Bacillus coli-communis and Streptococcus viridans predominate

average case, one may see ulcers in all stages of development—some small, round or oval, superficial ulcers, others irregular or deep and spreading, and still others in various stages of healing. In all cases, the mucosa is intensely congested. The mesenteric glands are rarely involved. The small intestine is rarely affected. Liver abscess is an unusual complication. Except possibly for a fatty liver, the remaining organs are in a surprisingly good state in the average case.

It might be well to mention, at this point, a condition often described as follicular colitis. Here the solitary follicles situated in the mucosa of the colon and rectum are the seat of lesion. The swollen follicles cause a pressure necrosis in the overlying mucosa giving rise to small, rounded, well defined ulcers, usually located along the line of the mesentery or of the longitudinal folds. This condition is fairly frequent in fatal nonspecific diarrheas of children.

Histopathology.—Sections of colon taken from ulcers and surrounding areas, show, first, an acute inflammation of the mucosa which becomes red, swollen and may be the seat of small hemorrhages. Numerous leukocytes are to be seen. The submucosa and muscularis are infiltrated with leukocytes and plasma cells. There is dilatation of the blood and lymph vessels. Soon the mucosa becomes necrosed and is cast off, leaving a very superficial ulcer. The epithelium of Lieberkühn's crypts may be only the seat of cloudy swelling, or else may be destroyed in the ulcerative process. The mucosa in other areas may be atrophic. Granulation and foreign body giant cells may be present in ulcerated regions.

In follicular colitis, the pathologic process is similar, except that it starts in the solitary follicles, which become hyperplastic and infiltrated with small round cells. The overlying mucosa becomes necrotic, and

Fig. 6.—Sigmoidoscopic picture in follicular ulcerative colitis; punched out appearance of ulcers, which correspond in position to solitary follicles.

the follicle ruptures, resulting in a discrete, superficial, round ulcer with a flat base.

THEORIES AS TO THE ETIOLOGY OF NONSPECIFIC ULCERATIVE COLITIS

Theories concerning the cause of this obscure condition are still rather vague, but we have often thought of several possibilities:

Constitutional.—The frequency with which this disease attacks run down, debilitated and insane persons suggests the possibility of some underlying constitutional factor. There may be absent from the wall of the colon, under abnormal conditions, certain substances which normally protect the mucosa against injury by harmful food substances or possibly digestive juices within the colon. Some have considered the condition in the insane as being essentially a trophic disturbance.

Traumatic.—The frequency with which intestinal mucosa is exposed to mechanical injury suggests this theory. There may be only a minute denudation of mucosa which could be caused by the edge of an apple seed or other débris. Yet this might be sufficient to give virulent pathologic organisms within the intestine an opportunity to obtain a foothold, and give rise to inflammation of the mucosa, or the bacteria may play a minor part and the digestive juices or proteolytic ferments give rise to an ulcerative process.

Excretory.—It is possible that toxic substances, metabolic or bacterial, excreted through the wall of the colon can result in ulcerative lesions. Flexner and Sweet [18] have shown this to be true for the toxin of *Bacillus dysenteriae.*

Bacterial.—As suggested in the discussion on the bacteriology of nonspecific ulcerative colitis, under abnormal conditions, pathogenic bacteria, which ordinarily lie dormant, may suddenly predominate in the intestinal flora and exert a direct harmful action on the wall of the intestine. Occasionally, one receives the impression that even *Bacillus coli,* under certain conditions, may become pathogenic. A point in favor of this theory is the report of success in some cases by the use of *Bacillus coli* vaccine.

TREATMENT

Medicinal.—These measures are directed chiefly toward influencing the bacteriology of the affected region and to relieve discomfort.

(*a*) Colon Irrigation: Colon irrigations have proved very effectual in our cases and bring about rapid relief or possible cure. Various substances have been used (silver nitrate, silver nucleinate, boric acid, physiologic sodium chlorid solution, sodium bicarbonate, quinin and water), but we have found potassium permanganate, peroxid of hydrogen and chloramin-T best. Of the the latter three, potassium permanganate irrigation is our method of choice. The colon should be as empty as possible before injection. The patient is placed in the knee-elbow position, with thighs perpendicular to the bed, back concave and shoulders resting on the bed (in order to reduce the natural obstruction at the sigmoidorectal flexure). The tip of the nozzle is introduced about 1½ to 2 inches (3.7 to 5 cm.) inside the rectum, and large quantities of potassium permanganate solution are injected—several quarts if possible. We start with 1:10,000 solution, and gradually work up to 1:5,000. The irrigations are given three times a day, and retained each time for an hour (this is more easily accomplished if the tube is left in position).

18. Flexner, S., and Sweet, J. E.: The Pathogenesis of Experimental Colitis, and the Relation of Colitis in Animals and Man, J. Exper. Med. **8**:514-535, 1906.

It is often surprising what a good result one may obtain by suddenly switching from permanganate to peroxid or chloramin-T. It is possible that these strong oxidizing agents affect the bacteria directly, especially the anaerobes.

(*b*) Diet: The idea is to endeavor to furnish a diet which will favor the development of normal intestinal bacteria. Thus, if the flora is essentially putrefactive, the proteid should be largely eliminated from the diet. So, too, in the fermentative diarrheas, the carbohydrates should be curtailed.

(*c*) Ingestion of Harmless Bacteria to Replace Harmful Flora: Herter [19] was the first to recognize the possibility of introducing desirable types of bacteria into the intestine. This method has practically

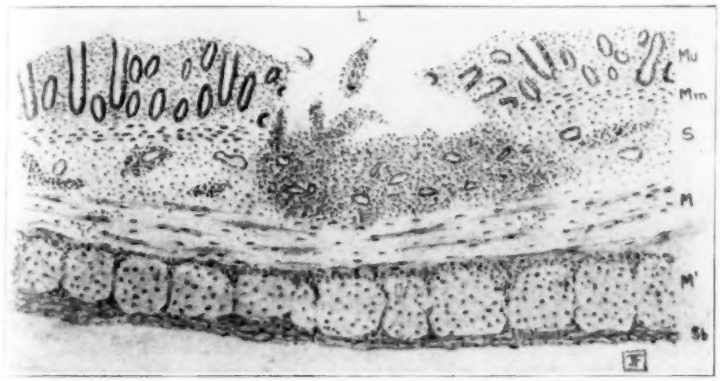

Fig. 7.—Histopathologic picture of typical ulcerated area in case of idiopathic ulcerative colitis; *L*, ulcerated area; *Mu*, mucosa; *Mm*, muscularis mucosae; *S*, submucosa; *M* and *M'*, muscularis, and *Sb*, subperitoneal connective tissue. In the process of healing, the necrotic tissue is removed, the area granulates and epithelializes over until, in most cases, restoration of normal contour is complete.

narrowed itself down to *Bacillus acidophilus*. This may be taken in whey or broth cultures, or in the form of acidophilus milk. The proteids in the diet should be cut down and large amounts of lactose administered to help assure permanence of these bacilli in the colon.

(*d*) Vaccine: Numerous observers have reported good results with *Bacillus coli* vaccine, preferably made up of many strains. Our experience has been very limited.

Serums and antitoxins should be theoretically useful, but, except in the case of bacillary dysentery, they have not yet been successfully

19. Herter, C. A.: On Certain Relations Between Bacterial Activity in the Intestine and the Indican of the Urine, Brit. M. J. **2**:1847-1849, 1897.

prepared. Morphin or other opium preparations have been used to relieve acute symptoms.

Surgical.—Various procedures have been used with more or less success. These are early appendicostomy or ileostomy, complete transverse colostomy and, in cases in which the entire colon is involved, colectomy.

Complete diversion of the intestinal contents or entire removal of the affected area seem to be the most logical procedures, but, unfortunately, these are usually accompanied by a rather high mortality. In cases not yielding to medicinal therapy, ileostomy is our method of choice. At a later period, colectomy is to be preferred.

CONCLUSIONS

1. A clinical and pathologic review of forty-one cases of nonspecific ulcerative colitis shows this affection to be a distinct clinical entity of obscure origin.

2. In our hands, the best results have been obtained by means of colonic irrigations.

Future studies will be mostly devoted to more detailed laboratory investigations, with a view to ascertaining a possible specific etiologic agent.

THE ELECTIVE LOCALIZATION OF BACTERIA IN PEPTIC ULCER*

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One of the numerous theories of peptic ulcer is that bacteria are an important etiologic factor. Just how great a part bacteria play is, however, a debated and undetermined question. Bevan [1] thinks that hematogenous septic infarcts of the mucosa may have a rôle but are not the common cause. Eusterman,[2] on the other hand, states that "the theory that infection is the cause of ulcer is admittedly the only tenable one at this stage of medical progress." Between those two diverse views is the classification of Smithies,[3] who divides ulcer from the standpoint of etiology into ten groups, and classifies one third of the total number as bacterial in origin.

Experimental data concerning the infectious theory of ulcer are due almost entirely to the work of Rosenow, who has shown that the intravenous injection of streptococci may be followed by ulcer of the stomach and duodenum; that streptococci are commonly found in the ulcer of man; and that the injection of streptococci isolated from the ulcer wall as well as from foci of infection in patients suffering from peptic ulcer produces, when injected into animals, ulcers of the stomach and duodenum resembling those of man.[4]

The best proof of a causal relationship of bacteria to systemic disease is the reproduction of the patient's lesion in animals by the injection of bacteria isolated from septic foci in the patient. Ability to so reproduce lesions is of interest not only as proof of an etiologic relation of the bacteria to the disease but also as evidence of a specific tendency of different strains of bacteria to cause certain diseases. Such a specific tendency is the elective localization of bacteria in the sense of Rosenow.

Rosenow, in a mass of experimental work, has produced convincing evidence to support the idea of elective localization. The theory has not found acceptance, however, at the hands of many other research workers largely because few have been able to verify Rosenow's experimental results. I have discussed elsewhere the literature concerning this point

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* From the Deaner Institute.

1. Bevan, A. D.: Relative Value of Surgical and Medical Treatment of Gastric and Duodenal Ulcer, J. A. M. A. **79**:22 (July 1) 1922.

2. Eusterman, G. B.: Minnesota Med. **6**:698 (Dec.) 1923.

3. Smithies, Frank: Significance of Etiologic Factors in Treatment of Peptic Ulcer, J. A. M. A. **74**:1555 (June 5) 1920.

4. Rosenow, E. C.: J. Infect. Dis. **19**:333 (Sept.) 1916; ibid. **19**:527 (Oct.) 1916. Rosenow, E. C.: Surg., Gynec. & Obst. **33**:19 (July) 1921. Rosenow, E. C.: J. Infect. Dis. **33**:248 (Sept.) 1923.

and reported a series of eye infections,[5] several cases of pyelonephritis[6] and two cases of multiple onychia[7] studied from the standpoint of elective localization. In these experiments, there was an unmistakable tendency of the bacteria to reproduce, on intravenous injection, the type of lesion from which the patient suffered. I have pointed out what is perhaps the fundamental obstacle to the reproduction of specific lesions in animals, namely, the failure of most workers to use culture mediums furnishing graded oxygen tension. This point has also been emphasized by Rosenow.

Recently, I have been studying a series of patients suffering from peptic ulcer to determine whether bacteria isolated from areas of dental infection in such patients would tend to produce gastroduodenal lesions in animals. The results are of interest from the standpoint of the theory of elective localization of bacteria and of the infectious origin of peptic ulcer.

Rosenow has reported, in several papers, his studies of elective localization in peptic ulcer. He found that 68 per cent. of 168 animals injected with thirty-seven strains of streptococci from patients with gastric ulcer had lesions of the stomach, while only 15 per cent. of a series of control animals injected with bacteria from patients with myositis had gastric lesions.[8] Nakamura,[9] working in Rosenow's laboratory, injected sixty-six animals with cultures from the tonsils in cases of gastric ulcer and found gastroduodenal lesions in 70 per cent. Similar lesions were found in 25 per cent. of control animals injected with tonsil cultures from other patients. Rosenow has made the observation[10] that the specific tendency to localize in the gastric mucosa may last as long as eight and one-half years, when the infecting bacteria are kept under anaerobic conditions. He also has found that the streptococci of ulcer produce free, in broth cultures and likewise in their substance, a poison that selectively injures the mucosa, since lesions can be produced by broth filtrates and by dead cultures.

METHODS

In the work here reported, I have followed closely certain fundamental technical details insisted on by Rosenow and usually disregarded by those attempting to repeat his work. All cultures have been made in glucose brain broth and glucose brain agar, mediums which provide every

5. Haden, R. L.: Elective Localization in Eye of Bacteria from Infected Teeth, Arch. Int. Med. **32**:828 (Dec.) 1923.
6. Haden, R. L.: Am. J. M. Sc., to be published.
7. Haden, R. L., and Jordan, W. H.: Arch. Dermat. & Syph. **8**:31 (July) 1923.
8. Rosenow (Footnote 4, second reference).
9. Nakamura, T.: Ann. Surg. **76**:29 (Jan.) 1924.
10. Rosenow (Footnote 4, third reference).

degree of oxygen tension. The exact method of preparation has been described elsewhere.[3] The original broth cultures have been injected into animals as soon as good growth was obtained. This was usually from fifteen to twenty-four hours after the culture material reached the laboratory.

Before extraction, the tooth to be cultured was scrubbed with gauze and painted well with tincture of iodin followed by alcohol. The area of operation was walled off with sterile gauze. After removal, the tip of the tooth was cut off with sterile forceps directly into a test tube containing a few cubic centimeters of sterile physiologic salt solution and a small amount of sterile sand. The tubes were then well shaken to macerate the tissue on the tip of the tooth as completely as possible. The mediums are inoculated by pouring the salt solution containing the suspended tissue into a deep tube of glucose brain agar previously heated and cooled to 40 C. The tube is quickly inverted twice and allowed to harden. The small amount of salt solution remaining in the tube is poured into a deep tube of glucose brain broth. The inoculated tubes are incubated from twenty-four to forty-eight hours. A smear is made from the broth culture and stained by Gram's method. A transplant of the broth culture is made to a blood agar plate. The appearance of a culture in a deep tube of glucose brain agar is shown in Figure 1, *B*. This culture is from the left lateral incisor shown in Figure 1, *A*. It is from one of the patients reported in this series (Case 1), and is of special interest in that the organism will not grow in the strictly aerobic portion of the tube. This organism would grow poorly, if at all, on open plates. Even if a culture on open plates were successful, it is very probable that the tendency to produce specific lesions would have been lost.

Rabbits have been injected intravenously with the original broth culture. When cultures were taken from several teeth from one patient the several broth cultures often were mixed before injection. The animals varied somewhat in size but averaged about 1,500 gm. Each animal was given 5 c.c. of the broth suspension.

The animals were killed from two to four days after injection, and carefully examined for lesions in all organs. No lesions were considered as present unless plainly visible to the naked eye of at least two observers. Microscopic sections were made from some of the tissues but not as a matter of routine.

EXPERIMENTAL OBSERVATIONS

Twelve patients have been studied. Streptococci were grown from the root tip of one or more teeth or from areas of infected bone in each case. In some cultures, staphylococci were recovered with the streptococci. The streptococci were usually of the nonhemolytic type. In only

one instance (Case 2) were hemolytic organisms found. Some of the nonhemolytic streptococci were of the green producing type, others were indifferent on blood agar.

Forty-five rabbits were injected intravenously with the broth cultures. At least two rabbits were injected from each patient. Twenty-four, or 53 per cent., of the animals showed at necropsy lesions in the stomach or duodenum or both, as shown in the accompanying table. There were positive findings in at least one animal from each patient. During the period covered by these experiments, 535 other rabbits were injected similarly with cultures from the dental foci of 191 patients not known to be suffering from peptic ulcer. Of these, forty, or 7 per cent., showed at necropsy lesions in the stomach and duodenum. This figure (7 per cent.) can be taken as the normal incidence of peptic lesions on routine intravenous injection apart from any specific tendency to localize.

Localization of Bacteria from Dental Infection on Intravenous Injection in Rabbits

			Percentage of Animals Showing Lesions in							
Group	Number Animals Injected	Number Patients	Joint	Muscle	Kidney	Endocardium	Myocardium	Stomach and Duodenum	Brain	Eye
1*	535	191	57	27	38	18	11	7	7	3
2†	45	12	36	27	22	9	18	53	4	11

* Group 1, animals inoculated with dental cultures from patients not known to be suffering from peptic ulcer.

† Group 2, animals inoculated with cultures from teeth of patients suffering from peptic ulcer.

The table details also the percentage of animals having lesions in other organs. The animals in Group 2 show a lower percentage of lesions in other organs, except the muscle, which is the same, and the myocardium, which is higher. In numerous instances in Group 2, the rabbits had no lesions other than those of the stomach and duodenum. The fact that many animals show other lesions also is no argument against the theory of specific localization. Many of the patients likewise presented symptoms of other systemic disease of focal origin coincident with the peptic ulcer.

The anatomic lesions, as observed grossly, were usually hemorrhagic with or without ulceration. The lesions in the stomach nearly always showed ulceration or at least erosion. The hemorrhage in the duodenum usually was not followed by gross ulcer formation. The course of the pathologic process after the initial injury depends largely perhaps on the amount of free hydrochloric acid present. In some animals, the lesions consisted principally of necrosis in the muscle wall, a type of lesion commonly found in the voluntary muscle of the rabbit after intravenous injection.

Sections of the involved parts show hemorrhage, polymorphonuclear infiltration and necrosis of the mucosa (Fig. 6). The pathologic process is usually quite diffuse and evidently not usually dependent on thrombosis or embolism. It is often assumed that damage here by bacteria must result from one or the other of these two conditions. A study of the sections does not bear out this assumption. This is especially true of duodenal lesions. Judd [11] has pointed out that very commonly patients diagnosed clinically as having duodenal ulcer are found, at operation, to have a diffuse duodenitis without ulceration. The lesion observed in the duodenum of animals is usually a duodenitis of such a type.

COMMENT

In this series, 53 per cent. of the animals showed lesions of the stomach and duodenum after the intravenous injection of bacteria recovered from chronic foci of infection in dental areas of patients suffering from peptic ulcer. Only 7 per cent. of animals similarly injected with cultures from patients not known to be suffering from peptic ulcer developed lesions of the stomach or duodenum. Such evidence is very strong proof of Rosenow's idea that the bacteria concerned in peptic ulcer show a specific tendency to localize in the gastroduodenal region. The findings thus support the theory of the elective localization of bacteria.

The experimental data reported here is also good evidence in favor of the infectious origin of peptic ulcer. The frequent manifest improvement in the patient's condition following the removal of chronic infection is the final link in the chain of evidence. Such improvement was apparent in many cases of this series.

Another point in favor of the causal relation of chronic focal infection to peptic ulcer and also of the theory of elective localization is the anatomic location of the gastric and duodenal lesions in the experimental animals. It is well recognized that gastric ulcer may occur in any part of the stomach but is much more frequent in the pyloric region. The experimental gastric lesions have a similar distribution. Clinically, duodenal ulcer is always limited to the first third of the duodenum. The usual explanation given for this localization is that only in this portion is free hydrochloric acid present, and that here the gastric contents are retained longer than in any other portion of the duodenum. In every animal but one in which duodenal lesions were observed, the involvement was limited to the duodenal bulb. The one exception was a very extensive lesion extending from the pyloric ring through the greater part of the duodenum (Fig. 4, *B*).

11. Judd, E. S.: Journal-Lancet **42**:381 (Aug. 1) 1922.

Several points in regard to the relation of dental infection to peptic ulcer should be emphasized. Not infrequently, infection in the maxilla or mandible at the site of extraction of teeth harbors organisms that are the cause of systemic disease. This is well illustrated in Cases 3, 5 and 10, in this series. Often the areas from which teeth are missing are not even roentgenographed.

Usually, the roentgenologist attempts to translate changes around the teeth, as revealed by the roentgen-ray examination, into terms of numbers of bacteria. Dental infection is often ruled out because there is not roentgenographic evidence of such infection. In cultures, by a quantitative method, of the root tip of over a thousand pulpless teeth, we have been able to demonstrate that the roentgenographic negative tooth harbors infection almost as frequently as the roentgenographic positive tooth.[12] It is apparent that a pulpless tooth should not be ruled out as a possible focus of infection on roentgenographic evidence alone.

A very important factor in focal infection is the frequent multiplicity of foci. Even when such a specific lesion as gastric ulcer is reproduced in animals by the intravenous injection of bacteria from a certain focus, it is quite possible that other foci might be present and equally active. Cases illustrating this point have been reported elsewhere.[13]

SUMMARY AND CONCLUSIONS

In a study of twelve cases of peptic ulcer from the standpoint of a possible causal relation of dental infection, cultures from foci of infection in dental areas were made in glucose brain broth and glucose brain agar to provide the optimal oxygen tension. The organisms recovered were streptococci in pure culture or associated with staphylococci.

Fifty-three per cent. of forty-five rabbits injected intravenously with the broth cultures from the twelve patients showed, at necropsy, gross lesions of the stomach or duodenum.

Seven per cent. of 535 rabbits injected intravenously with cultures from dental infection of 191 patients not known to be suffering from peptic ulcer showed similar lesions.

The experimental duodenal lesions are practically always confined to the duodenal bulb.

The results here reported furnish confirmatory proof of Rosenow's theory of elective localization and the infectious theory of peptic ulcer.

Dental infection is an important factor in the causation of gastric and duodenal ulcer.

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12. Haden, R. L.: Radiology, to be published.
13. Haden, R. L.: M. Clin. N. A. **7**:1109 (Jan.) 1924.

REPORT OF CASES

CASE 1.—J. J. W., aged 32, a plumber, gave a typical history of recurring attacks of duodenal ulcer over a period of six years. The present attack had begun five weeks before he was first seen and had been unusually severe. He was in a good state of nutrition. The tonsils were small, and no pus could be expressed. The heart sounds were clear; the pulse was 80-100; the systolic

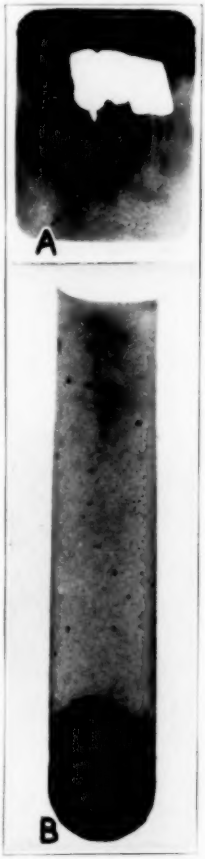

Fig. 1.—*A*, lateral incisors, Case 1; *B*, culture tube of left lateral incisor, indicated by arrow in *A*.

blood pressure 140, the diastolic 100; the lungs were negative. There was tenderness in the epigastrium.

The roentgenograms of the teeth showed large areas of bone absorption around the lower right and left lateral incisors (Fig. 1, *A*). Cultures showed a profuse growth of streptococci which would not grow to the top of the culture tube (Fig. 1, *B*). There was also an area of questionable infection at the site of extraction of another tooth.

Animal Inoculations.—Two rabbits were infected with the mixed cultures from the two incisor teeth. Both were killed the following day. One showed a massive hemorrhage in the duodenal bulb (Fig. 2, *A*) with no lesions elsewhere. The other showed one moderate sized hemorrhage in the first third of the duodenum and a slight purulent arthritis, with no other lesions. One rabbit injected with the broth culture from the bone showed only slight involvement of the joints.

Case 2.—W. T. G., aged 43, business man, complained of a dull, burning sensation in the epigastrium, in October, 1922. The trouble came on one-half to two hours after meals and was relieved by food or soda. He had frequent heartburn but no acute pain or vomiting. The physical examination was negative, except for tenderness at the tip of the ninth rib in front, and several

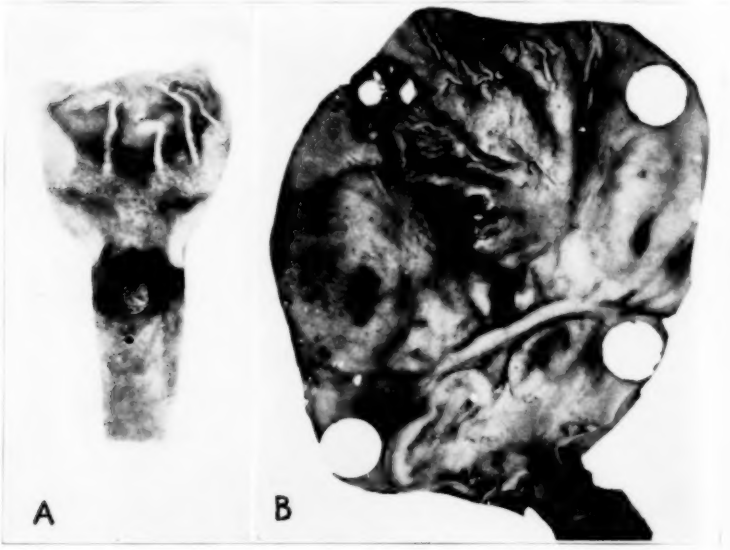

Fig. 2.—*A*, duodenum of rabbit, following the injection of streptococcus recovered from the two lateral incisors shown in Figure 1; *B*, stomach of rabbit following intravenous injection of culture from cuspid shown in Figure 3, *B*.

pulpless teeth. The tonsils had been removed. The patient became symptom free on a special diet, until April, 1923, when he presented typical symptoms of a duodenal ulcer. Gastric analysis showed free hydrochloric acid, 40 per cent. acidity, and total acid, 65 per cent. acidity. The roentgenographic examination showed marked deformity of the duodenal bulb. The symptoms again disappeared under treatment. Roentgenograms of the teeth, at this time, showed three pulpless teeth with root canals completely filled. All had some bone absorption around the root tip. The three teeth were extracted. Cultures of all in deep tubes of glucose brain broth showed many colonies of bacteria.

Animal Inoculations.—Two rabbits were injected with the broth culture from each tooth. Two animals showed no lesions anywhere and two, purulent fluid in the larger joints. The two rabbits injected with the culture from the upper right lateral incisor (Fig. 3, *B*) died the day following injection. There were

many hemorrhagic areas with erosion in the stomach, some of which had progressed to ulceration (Fig. 2, *B*). Three other animals were injected with the same organism in doses down to 0.5 c.c. All showed, at necropsy, hemorrhages in the gastric mucosa.

CASE 3.—H. A. A., aged 44, a business man, had several gastric hemorrhages, in December, 1922. For six months previous to this, he had had indigestion, consisting principally of a feeling of fulness after eating. A diagnosis of duodenal ulcer was made. Several teeth were extracted at this time. Rest in bed for one month, milk diet and alkalis entirely relieved the symptoms. The patient states that he still has indigestion, at times, for which he takes soda.

Roentgenograms, in June, 1924, showed one tooth of questionable vitality and one pulpless tooth with little roentgenographic evidence of infection. At the site of extraction of the upper left first bicuspid and first molar, some filling material remained, and the surrounding bone showed evidences of infection (Fig. 3, *C*). The two teeth were extracted and the infected bone curetted. Cultures in deep tubes of glucose brain broth agar showed a short chain streptococcus in all.

Fig. 3.—*A*, first molar, showing no roentgenographic evidence of infection. The culture showed an anaerobic streptococcus, which produced gastric lesions on intravenous injection (Case 9). *B*, cuspid and first bicuspid, Case 2, both showing evidence of infection. Both teeth showed a profuse growth of organisms on culture. The organisms from the cuspid tooth produced no gastric lesions, while those from the cuspid caused very marked lesions (Fig. 2, *B*). *C*, small bits of gutta percha remaining at the site of extraction of infected teeth, surrounded by an area of infected bone (Case 3). A pure culture of green producing streptococci was grown from the curettings, which, on injection, caused the lesion shown in Figure 4, *B*.

Animal Inoculation.—Two rabbits were inoculated with the mixed broth cultures. One rabbit was dead the following morning and showed many hemorrhages in the duodenum. The second rabbit was killed. This one also showed many hemorrhages in the first third of the duodenum without lesions elsewhere (Fig. 4, *A*).

In order to determine whether the area of infected bone might play a part in the causation of the peptic ulcer, one rabbit was injected with 5 c.c. of the broth culture from this area alone. At necropsy, twenty-four hours later, the duodenum showed massive hemorrhages (Fig. 4, *B*). There were no other lesions.

CASE 4.—S. T., aged 50, a coal dealer, stated that he had had three attacks of pain in the epigastrium, coming on one or two hours after meals. The pain occurred also at night, and was relieved by food or soda. There was

no nausea or vomiting. The present attack began three weeks before admission. He had noticed some irregularity of the heart for ten years. The previous history was negative, except for occasional attacks of rheumatism and gallstone colic ten years before. The tonsils had been removed.

On examination, the heart action was persistently irregular; the blood pressure was 120; the lungs and abdomen were negative. There were many crowned teeth; the urine examination was negative; the hemoglobin was 80 per cent., and white corpuscles totaled 14,000. The fluoroscopic examination showed forceful peristaltic waves and a deformed duodenal cap. A diagnosis of duodenal ulcer and auricular fibrillation was made.

Animal Inoculations.—Six rabbits injected with the broth culture from the lower teeth and nine upper teeth showed no lesions anywhere when killed, twenty-four hours after injection. One rabbit injected with the mixed cultures

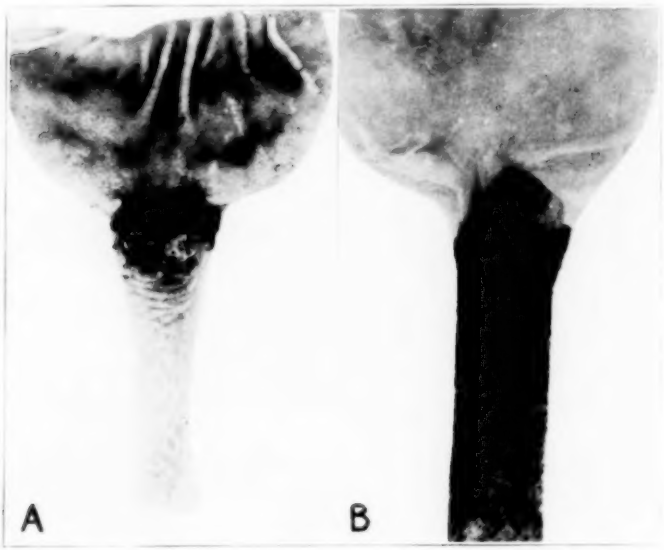

Fig. 4.—*A*, lesion in duodenum following the intravenous injection of mixed cultures, Case 3; *B*, extreme involvement of duodenum following the injection of streptococcus from area of residual infection (Fig. 3, *C*).

of streptococci from the upper left central, lateral and cuspid showed about 100 hemorrhages in the first third of the duodenum and a few hemorrhages in the wall of the pyloric end of the stomach. The only other lesions found were a few small areas of necrosis in the muscle.

Within ten days after extraction, the heart action returned to normal and has remained so. The stomach symptoms also cleared up.

Case 5.—G. W. P., aged 47, a merchant, complained of abdominal pain of ten years' duration. He stated that he had had attacks of "dyspepsia" for eight or ten years. For six months, he had suffered from an aching pain in the epigastrium occurring two to three hours after meals. He was occasionally awakened at night. The pain was relieved by food or soda. He had been on a milk diet for six months with relief from pain, except at night.

The general examination was negative. The Wassermann reaction was negative. The blood and urine examinations were negative. Roentgenographic examination showed a duodenal ulcer. Gastric analysis showed free hydrochloric acid, 60 per cent. acidity, and total acid, 100 per cent. acidity. Operation, March 26, 1924, confirmed the diagnosis of duodenal ulcer. The appendix was removed, and a posterior gastro-enterostomy done.

Roentgenograms of the teeth showed several teeth with bone absorption around the root tip and an area of residual infection.

Animal Inoculations.—Two rabbits were injected with a culture from the residual area. One showed some lesions in the kidney medulla. The other showed hemorrhage and ulceration in the pyloric end of the stomach, and a few hemorrhages in the lumbar muscles. Two rabbits injected with the culture from the tooth showed lesions in the kidney medulla of both and purulent fluid in the joint of one.

Case 6.—J. A. L., aged 62, a lawyer, complained of headache, a tired feeling, and a dull ache in the epigastrium. He stated that the headache had troubled him for a number of years. The first attack of stomach trouble had occurred in 1908, and was characterized by pain in the epigastrium coming on one hour after meals. The pain was relieved by taking food. He had had numerous attacks and was just recovering from one when first seen. There had been no nausea or vomiting. The general physical examination was negative. The blood pressure was 125 systolic, 80 diastolic; the red cells totaled 5,120,000, the white cells, 8,100, and the hemoglobin was 100 per cent. The urine showed albumin and a few granular casts. The specific gravity was 1.035. The blood urea nitrogen was 29.5 mg. per hundred cubic centimeters, and the phenolsulphonephthalein test showed an excretion of 53 per cent. in two hours. A diagnosis of chronic nephritis, cholelithiasis and duodenal ulcer was made.

Several infected teeth were extracted. Cultures showed only a green producing streptococcus.

Animal Inoculations.—Two rabbits were injected with the mixed cultures. One animal died the night following the injection and, at necropsy, showed no localized lesions. The other rabbit was killed three days after injection. There were many hemorrhages in the pyloric end of the stomach. There also was purulent fluid in the joints, some areas of necrosis in the voluntary muscle, numerous areas of necrosis in the muscle wall of the pyloric end of the stomach, abscesses in the medulla of the kidney and involvement of the heart muscle and pericardium.

Case 7.—R. McC., aged 47, a clerk, complained of pain in the epigastrium. He had always been well except for an attack of influenza, in 1918. The epigastric pain had occurred intermittently for five years. It came on about two hours after meals, and was relieved by food or soda. The physical examination was negative, except for tenderness in the epigastrium and numerous crowned teeth. The urine was negative. The blood count showed 4,200,000 red cells, 9,000 white corpuscles and 90 per cent. hemoglobin. The gastric analysis showed a total acidity of 95. A clinical diagnosis of duodenal ulcer was made. Feb. 14, 1923, four pulpless teeth were extracted.

Animal Inoculations.—Two rabbits were injected with the mixed cultures. One died, two days later. There was some pericorneal injection. The necropsy showed many hemorrhages in the first third of the duodenum. The second rabbit was killed, two days after injection. One large hemorrhage in the mucosa of the fundus of the stomach was found. There also were a purulent arthritis and abscesses in the kidney medulla and myocardium.

Case 8.—G. B., aged 72, a financier, was first seen following a copious gastric hemorrhage. He was in an excellent state of nutrition, was very active,

and had never been ill previously. The present illness had begun, shortly before, with a fainting attack followed by the vomiting of a large amount of blood. He also passed blood in the stools. The roentgenographic examination of the stomach showed no abnormality. The Wassermann reaction was negative. The physical examination was negative, except for the evident anemia and some tenderness over the spleen. The blood count showed 2,100,000 red cells, white corpuscles and 42 per cent. hemoglobin. The patient made a gradual recovery without further gastric symptoms.

A roentgenogram of the teeth showed four pulpless molar teeth, only one of which had an area of bone absorption around the root tip.

Animal Inoculations.—Cultures from the upper right first and second molars showed, in deep tubes of glucose brain broth agar, a very large number of colonies of a gram-positive diplococcus. One rabbit injected with the culture from the first molar showed no gastric lesion. Two rabbits were injected with the culture from the second molar. One showed many hemorrhages in the mucosa of the stomach. There were no other lesions, except a few hemorrhages in the myocardium. The second rabbit showed no lesions. The lower

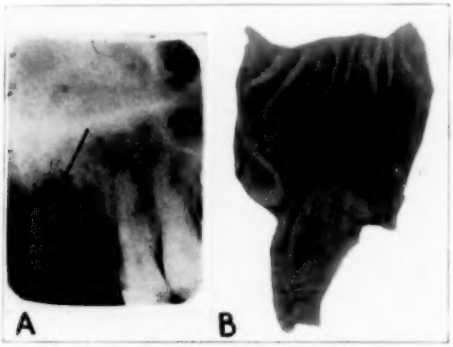

Fig. 5.—*A*, area of infected bone at the site of extraction of infected tooth, the culture from which showed a streptococcus; *B*, ulcers in stomach of rabbit produced by the intravenous injection of the organism recovered from the area in *A*, Case 10.

right second molar and the upper left first molar were extracted several days later. Both showed, on culture, a profuse growth of diplococci. Two rabbits were injected intravenously with the mixed cultures. Both, at necropsy two days later, showed hemorrhage in the first third of the duodenum with no lesions elsewhere.

Case 9.—C. T. C., aged 26, a medical student, complained of a duodenal ulcer. He had always enjoyed excellent health before his present illness, except for some rheumatic pains which had been relieved by tonsillectomy. The present trouble began soon after the tonsillectomy, in March, 1923, with epigastric pain, occurring before meals and about two hours after meals. The pain was relieved by food or alkalis. A fluoroscopic examination, in December, 1923, showed definite signs of a duodenal ulcer. Under alkalis and dietetic treatment, he improved.

The dental roentgenograms revealed three pulpless teeth, none of which showed roentgenographic evidence of infection. March 19, two of the teeth

were removed. Two rabbits injected with the broth cultures showed no lesions anywhere. Several days later, the left lower first molar (Fig. 3, *A*) was extracted. A pure culture of a short chain streptococcus growing out in the anaerobic portion of the culture tube was obtained. Two rabbits were injected. Both, at necropsy, showed hemorrhage and ulceration in the pyloric end of the stomach. There were also necrosis in the muscles, vegetations on

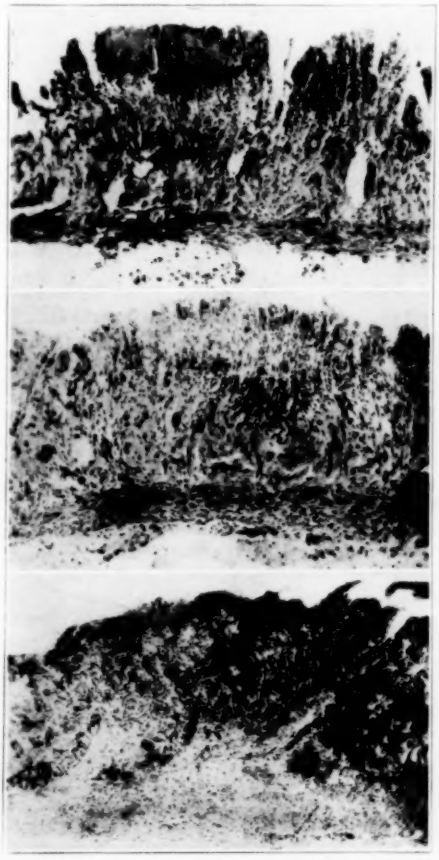

Fig. 6.—Peptic lesions produced by the intravenous injection of bacteria from dental infection: above and middle, stomach; below, duodendoum. There is marked hemorrhage, necrosis of the surface and polymorphonuclear infiltration.

the heart valves in one, and purulent fluid in the joints, cortical kidney abscesses, pericorneal injection and white streaks in the muscle of the other.

Case 10.—E. W. M., aged 25, an elevator constructor, complained of pain in the stomach, stating that he had had an attack of epigastric pain lasting several weeks, in 1921. He had never had any other serious illness. His present attack had begun six weeks before admission, and was characterized

by a gnawing pain in the epigastrium coming on before meals and relieved by food and soda. He was kept awake at night by the pain.

The patient was a well nourished, athletic individual. The tonsils had been removed. The physical examination was essentially negative. The blood count showed 3,584,000 red blood cells and 11,900 leukocytes. The stool was negative for occult blood. The meal showed 18 per cent. acidity, free hydrochloric acid and 60 per cent. acidity total hydrochloric acid at the end of an hour.

The dental roentgenograms showed three pulpless teeth all presenting evidence of infection.

Animal Inoculations.—Two rabbits each were injected with the cultures from the left lower central incisor, upper left cuspid and upper left first molar. Two were killed, and one died twenty-four hours after injection and showed no lesions at necropsy. Three were killed forty-eight hours after injection. One showed hemorrhage in the first part of the duodenum and lesions in the kidney medulla. One showed only muscle lesions; the other, muscle lesions, an ulcer in the pyloric end of the stomach, and slight joint involvement.

One month after the first teeth were extracted, an area of infected bone in the region of the upper right cuspid was curetted. A profuse growth of streptococci was obtained in the deep agar tube. One rabbit was injected with broth culture. At necropsy, two days later, there were multiple hemorrhages and beginning ulceration in the pyloric end of the stomach. There also were abscesses in the kidney medulla, hemorrhagic areas in the muscles and the myocardium, and small vegetations on the mitral valve.

Case 11.—Mrs. G. E. S., aged 33, a housewife, stated that her stomach trouble had begun, ten months before, with pain in the abdomen, occurring about one-half hour after meals, and also a gnawing pain two to three hours after eating. She was often awakened at night with the pain. Her tonsils had been removed, in 1917. She had had pneumonia with empyema, in 1904, but had been well for ten years preceding the present illness.

The general physical examination was negative. The red blood cell count was 4,312,000, the hemoglobin 90 per cent., and the white count, 8,100. The gastric test meal showed: free hydrochloric acid 8 per cent. acidity and 29 per cent. total acidity.

The dental roentgenographs showed one tooth, the left upper first bicuspid, of questionable vitality. The left upper second bicuspid was pulpless, but showed no area of rarefaction of bone at the root tip. There was an area of residual infection at the site of extraction of the left lower first molar. The two bicuspids were cultured together and showed a profuse growth, in pure culture, of a green producing streptococcus. A pure culture of the same organism also was obtained from the area of infection.

Animal Inoculations.—Two rabbits were injected with the mixed broth cultures. One showed, at necropsy, hemorrhage and erosion in the pyloric end of the stomach, medullary lesions in the kidney and purulent exudate in the joints. The other showed numerous ulcerated hemorrhagic areas in the pyloric end of the stomach, a purulent arthritis, lesions in the kidney medulla and a few areas of infection in the muscles.

Case 12.—I. A. P., aged 50, a housewife, gave a typical history of duodenal ulcer, with recurrent attacks over a period of fifteen years. The epigastric pain was dull gnawing in character, and came on two to three hours after meals and during the night; the present attack had begun six weeks previously.

The patient was rather obese. There was tenderness in the epigastrium. The gastric analysis showed: free hydrochloric acid 27 per cent. acidity, and total acid, 51 per cent. acidity. The stool was negative for occult blood. The blood count was normal.

The roentgenogram showed two pulpless teeth, the left lower first and second bicuspids. A culture in the deep agar tube of the first bicuspid showed 50 colonies of a green producing streptococcus, the second bicuspid, a profuse growth of a similar organism.

Animal Inoculations.—Two rabbits were injected with the mixed cultures from the two teeth. One, at necropsy, showed no lesions, the other, a very marked involvement of the muscle wall of the pyloric end of the stomach extending through to the mucosa. There also was purulent fluid in the joints, lesions in the kidney medulla and some areas of necrosis in the voluntary muscles.

EXPERIMENTAL MORPHIN POISONING *

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The incentive to the experimental work described here in detail was provided by the investigations of Valenti,[1] in 1914. The work was actually begun in 1920 but, owing to circumstances over which we had no control, it was discontinued and resumed only in February, 1923.

A great deal of investigation has been carried on with morphin poisoning, and an excellent résumé has been presented by Du Mez.[2] It is clear that the opinion regarding the action of this alkaloid and its manner of destruction, or at least its alteration, in the animal body is a matter of considerable dispute.

At the present time and, as a matter of fact, ever since the Harrison Act went into effect, the problem of drug addiction and of handling addicts has been of sufficient gravity to attract the attention of a large number of investigators. On account of the conditions brought about by the enforcement of this act, interest has been renewed in the scientific investigations into the ultimate cause of morphin addiction. In general, this experimental work has been carried on with the lower animals being used as subjects. In many respects, the parallelism between morphin poisoning under experimental conditions in dogs, rabbits, guinea-pigs, rats or mice and that in the human being is by no means complete. This is notably the case during the withdrawal period, which presents the most characteristic symptoms in the human being. With animals, particularly with dogs, so far as our experiment goes, this does not hold true in any sense of the word. The popular periodicals have drawn considerable attention to the fact that Valenti succeeded in producing canine addicts presenting all the characteristics of morphin poisoning and even showing a desire for repeated injections when morphin had been withdrawn for some time. In other words, the overzealous but

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1. Valenti: Arch. f. exper. Path. u. Pharmakol., March 5, 1914.

2. Du Mez, A. G.: Increased Tolerance and Withdrawal Phenomena in Chronic Morphinism, J. A. M. A. **72**:1069 (April 12) 1919.

inaccurate and unscientific writer of the articles adopted Valenti's conclusions to his own ends, which were certainly not justified, as is seen when we refer to the work itself.

Our original plan was conceived with several objects in view. Primarily, we were interested in determining whether arrhythmia or other disturbance in heart function was produced during the abstinent period of habituated dogs. It was expected that the electrocardiograph would confirm or refute this point without the sacrifice of the animal. Secondly, it was anticipated that in the event arrhythmia or other cardiac irregularity was found to occur, the serum from such animals was to be injected into normal dogs, in order to confirm the second step of Valenti's work, viz., that some substance circulates in the blood stream which is responsible for the heart disturbances. Thirdly, it seemed desirable to use the serum of dogs containing this toxic substance which undoubtedly would be of a protein nature, and by injecting it into normal animals produce an antibody. It was hoped that this antibody would immediately relieve the cardiac disturbances in the withdrawal period. We now know, from the work of Pellini and Greenfield,[3] that this substance does not exist.

ELECTROCARDIOGRAMS

For our purpose, three healthy dogs were selected, weighing respectively 16 pounds, 3 ounces (7,349 gm.); 13 pounds, 4 ounces (7,377 gm.), and 22 pounds, 1 ounce (7,292 gm.). The injections were begun, March 1, 1923, with an initial dosage of 20 mg. The dosage was gradually increased until, July 20, each dog was receiving 650 mg., or 10 grains daily. All dogs were therefore subjected to the action of morphin for a period of four months and twenty days. Dog 1 received a total of 54.2 gm. (833.5 grains); Dog 2 received 51.756 gm. (798.6 grains), and Dog 3 received 53.744 gm. (829.3 grains). The last dose was given the afternoon of July 20. The next day, an electrocardiogram was made from each dog. This was repeated July 24, and again July 26.

Twenty-four hours were allowed to elapse following the last administration of the drug in order to promote the development of the same conditions under which the dog existed while being morphinized. It was believed that this would be sufficient time for the absorption of the dose from the subcutaneous tissue, and would not be too long a period for the initial symptoms to establish themselves. Forty-eight hours (the third day) from the last dosage should have been sufficient time for the

3. Pellini, E. J., and Greenfield, A. D.: Narcotic Drug Addiction, Arch. Int. Med. **33**:547 (May) 1924.

withdrawal symptoms to develop. They should reach a maximum on the fifth day, i. e., July 25, when the dogs would probably have eliminated or destroyed all the morphin which had been injected. We could not observe in these electrocardiograms any signs of arrhythmia or variability attributable to prolongation of the abstinence period, and certainly arrhythmia or serious cardiac disturbances would have been evident with such a sensitive instrument had they been present. It is true that in Dog 3 the third electrocardiogram showed a reversal of the T wave (Figs. 1, 2 and 3). This evidence did not warrant, nor would circumstances permit, our carrying out the other steps of our program.

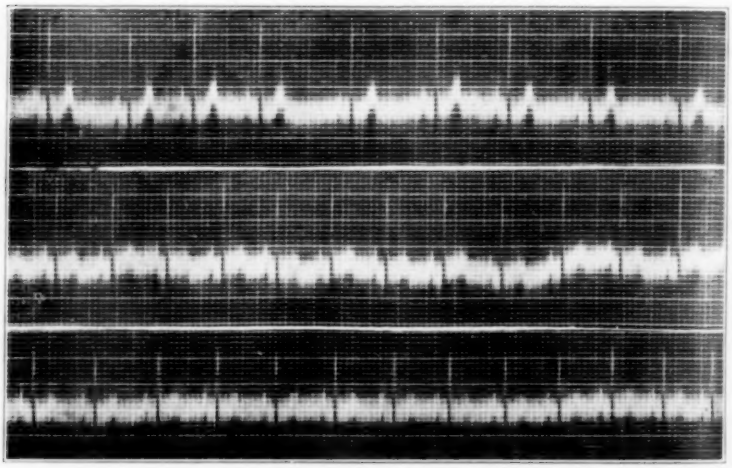

Fig. 1.—Lead III, Dog 1, July 21, 23 and 25, 1923, during abstinence period.

July 31, by an oversight, each dog again received an original dose of 10 grains, or 650 mg., and the next day, August 1, Dogs 1 and 2 were dead, while Dog 3 barely survived. Injections of Dog 3 were continued up to Jan. 29, 1924, the dog at times receiving as high as 2.145 gm. (33 grains) in a single dose. For some unknown reason, it died on the night of January 29, when we were preparing to make another series of electrocardiograms. This dog had received altogether, between March 1, 1923, and Jan. 29, 1924, 148.554 gm. (2,755.1 grains) of morphin sulphate.

We are well aware of the fact that dogs can survive remarkably large doses of morphin; nevertheless, during previous experiments, we have found it very advisable to begin with a very small dosage and to increase it gradually until what seems to be a refractory period has

been overcome. The amount could then be increased quite rapidly. One is not always successful even with small doses, as we learned from experiments in 1921, when three dogs were killed with comparatively small amounts of morphin repeated over a period of approximately thirty days. It seems possible that death was due to pyelitis, for which the constipated condition of the animals was directly responsible.

Never, at any period of the administration, have we been able to observe a dog showing a desire for the alkaloid comparable to that exhibited by human beings. On the contrary, almost invariably there was a reaction following each injection, and the dogs would complain bitterly, unless stuporous from the previous dose. Neither could we

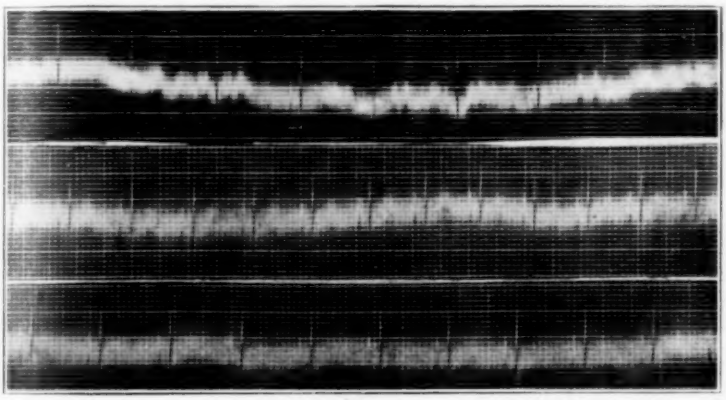

Fig. 2.—Lead III, Dog 2, July 21, 23 and 25, 1923, during abstinence period.

observe any nervous symptoms or signs of extreme agitation during the abstinence period. This refutes completely the popular statement that a dog could be converted into an addict and act in the same manner as a human being would act. We found no evidence that such was the case.

BLOOD EXPERIMENTS

As Morgenroth [4] and a number of other investigators have apparently demonstrated the capacity of the red cells to absorb quinin from the plasma, it was thought possible that the same phenomenon might hold true for another alkaloid, morphin. Furthermore, the hypothesis that the red corpuscles destroy or alter morphin so as to render it inactive is not altogether untenable.

4. Morgenroth: Deutsch. med. Wchnschr. **44**:961; 988, 1918.

For our purpose, the blood of a dog which had received daily injections of morphin sulphate from Feb. 1 until June 19, 1924, was used. These injections began with 32 mg. (one-half grain), and increased to 650 mg. (10 grains), the latter amount being administered for more than six weeks. The dog received a total of 26.378 gm. (407 grains) during the entire period.

June 29, 10 c.c. of blood was removed from the heart and defibrinated; the serum and blood cells were separated, and the latter thoroughly washed with physiologic sodium chlorid solution. Blood cells, serum and controls, with varying quantities of morphin, were arranged according to the scheme given in the accompanying table.

Arrangement of Blood Cells, Serums and Controls in Experiments with Morphin

	Serum	Saline Solution	Red Cells	Morphin Solution*
Row 1	0.5 c.c.	0.5 c.c.	.....	0.1, 0.2, 0.3, 0.4 c.c.
Row 2	0.5 c.c.	.....	0.5 c.c.	0.1, 0.2, 0.3, 0.4 c.c.
Row 3	0.5 c.c.	0.5 c.c.	0.5 c.c.	0.1, 0.2, 0.3, 0.4 c.c.

* One cubic centimeter contained 65 mg. (1 grain) of morphin sulphate.

The tubes were allowed to stand at 37 C., for two hours, in a water bath and were then placed in the icebox over night.

The method used in extracting the morphin was that of coagulation with heat and a faint excess of acetic acid; the filtrate was then evaporated from the coagulum and the residue extracted repeatedly with Prollius' mixture (ether, 65 parts; alcohol, 5 parts, and strong ammonia, 1 part). The red cells in Rows 2 and 3 were, of course, separated from the serum and saline and thoroughly washed until the washings showed no trace of alkaloid. They were then coagulated, filtered and extracted.

The results were entirely negative so far as absorption by the red cells was concerned. With the exception of the very faintest traces in two tubes in Row 2, of 0.3 c.c., and in Row 3, of 0.4 c.c., which were doubtful, no morphin could be detected in the blood cells themselves. It was readily separated from the serum and saline with which the cells had been mixed.

PROTECTIVE SUBSTANCES IN THE BLOOD

The results obtained by Hirschlaff [5] indicated, at least to himself, that an antibody was formed when morphin, in gradually increasing doses, was injected into animals. His tables show that in many cases he succeeded in saving the lives of animals by injecting them with

5. Hirschlaff, L.: Berl. klin. Wchnschr. **39**:549, 1902.

serum from a morphinized rabbit. He also tried his serum on an acute case of opium tincture poisoning, and the person was apparently saved by its action.

Hirschlaff cites the work of Gioffredi, who obtained similar results with cats and a dog. The serum prepared by Gioffredi is said to have saved a dog after double the lethal dose of morphin.

Morgenroth[6] repeated Hirschlaff's experiments with both rabbit and goat serum. He points to numerous fallacious deductions of Hirschlaff, notably the incorrect lethal dose for mice and the distinct protective influence of rabbit serum. Pellini and Greenfield[7] have shown that no protective substance exists in the serum after either human or canine morphin poisoning.

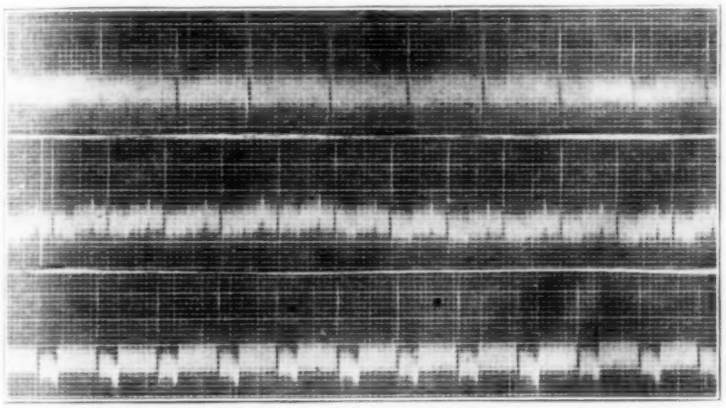

Fig. 3.—Lead III, Dog 3, July 21, 23 and 25, 1923, during abstinence period.

With these and similar observations in mind, we decided to test the protective action of defibrinated blood drawn from Dog 4 on a normal animal.

Accordingly, June 21, i. e., five months and twenty days from the beginning of the experiment and after two days of morphin abstinence, 50 c.c. of blood were drawn from the heart, under sterile precautions, and defibrinated.

To 10 c.c. of this blood were added 195 mg. (3 grains) of morphin sulphate in solution. This was allowed to stand on ice for twenty-four hours, and the entire amount, 13 c.c., was injected subcutaneously into

6. Morgenroth: Berl. klin. Wchnschr. **40**:471, 1903.

7. Pellini, E. J., and Greenfield, A. D.: Formation of Protective Substances Against Morphin, Arch. Int. Med. **26**:279 (Sept.) 1920.

a normal dog, weighing 20 pounds, 5 ounces (9,214 gm.). One day prior to this injection, it was determined that a control of 10 c.c. of untreated blood produced no reaction.

The morphin blood mixture was administered at 3:15 p. m., June 23. In about five minutes, vomiting occurred, with moderate salivation. Then, gradually, the animal lapsed into a stuporous condition, from which it could be aroused with difficulty only to subside immediately on the floor.

At 9:30 a. m., June 24, the animal was still drowsy and stuporous, but less so than the night before. June 25, the animal had completely recovered. The absorption at the site of injection was very slow, and the wheal still persisted, even though the morphin symptoms had disappeared. We could not conclude from our observations that the blood offered any protection whatever or mitigated the symptoms in the least.

ALTERATION OF MORPHIN IN VIVO

A number of investigators, notable among whom are Faust, Cloetta and Marmé,[8] have held that morphin was converted by the body into the oxidation product variously called oxydimorphin, dihydromorphin and pseudomorphin. Some workers claim to have detected the presence of this substance in the excreta of animals poisoned with morphin, one (Marmé) holding that the abstinence symptoms were caused by it. According to Du Mez and Valenti, Albanese proved that the livers of morphinized dogs were capable of destroying, or at least of altering, the constitution of morphin.

Another point in this connection was the supposition of Valenti that morphin was destroyed soon after injection because he failed to find a trace of the alkaloid in 50 c.c. of blood four hours after injecting 40 c.c. of 5 per cent. morphin solution (2 gm.) into the external jugular vein.

The experiment decided on was intended to, at least partially, reduplicate this work. Dog 4, after forty-eight hours of abstinence, was selected for this purpose, and the work was carried out under ether anesthesia. For the sake of clarity, this experiment may be divided into three parts:

(*a*) Six hundred and fifty milligrams (10 grains) of morphin sulphate was injected into the portal circulation. About eight minutes later, 45 c.c. of blood was removed directly from the heart.

(*b*) The hepatic and portal veins were ligated, and the liver was removed. The liver was connected with a cannula and perfused with

8. Acquired Tolerance of Morphin, editorial, J. A. M. A. **66**:657 (Feb. 26) 1916. Faust, E. S.: Arch. f. exper. Path. u. Pharmakol. **44**:217, 1900. Cloetta, M.: Ibid. **50**:453, 1903. Marmé: Deutsch. med. Wchnschr. **14**:197, 1883.

distilled water through the portal system until the wash water amounted to approximately 1,000 c.c. and gave no alkaloidal reaction.

(*c*) The liver was ground up fine and 325 mg. (5 grains) of morphin in solution was mixed thoroughly with 200 gm. The mixture was allowed to stand in the icebox for forty-eight hours.

RESULTS

The 45 c.c. of blood (*a*) was evaporated to dryness. The residue was ground up fine and repeatedly extracted with hot alcohol containing ammonia. This residue was moistened with hydrochloric acid, filtered and again evaporated. A test for morphin with Froehde's reagent was faintly positive. There was a faint greenish tinge to the coloration. Both Mayer's alkaloidal reagent and iodin potassium iodid solution gave positive reactions.

The wash water obtained by perfusing the liver (*b*) was coagulated with dilute acetic acid and heat, and, after being filtered, was evaporated to dryness. The residue was extracted repeatedly with alcohol and ammonia, evaporated and weighed. The yield was 48 mg. This was acidified with hydrochloric acid and carefully evaporated. Tests for morphin with Froehde's reagent and formaldehyd sulphuric acid were positive with a tendency to turn green, said to be a characteristic test for oxydimorphin. Obviously, the morphin had been changed in the liver capillaries and apparently much was destroyed, unless it had succeeded in gaining access to the general circulation before the connection was ligated.

The liver morphin mixture (*c*) yielded the best and the most interesting results, besides apparently confirming the work of Albanese already mentioned.

This mixture was coagulated with heat and acetic acid, filtered with a Buchner funnel, and the filtrate evaporated to dryness in the water bath. The residue, which was considerable, was repeatedly extracted with hot ammoniacal alcohol. The exhaustion of the residues from repeated extraction was completed three times, the final yield being soluble in hot alcohol and insoluble in water. The last extraction, when evaporated, yielded a residue which, while colored, was obviously nearly pure, since it was almost entirely crystalline. It could be divided, by treating with Prollius' mixture, into two parts, which together amounted to 147 mg. of morphin, equivalent to 319 mg., or 4.9 grains, of crystalline morphin sulphate.

Both parts gave strong reactions for morphin with Froehde's reagent and with formaldehyd sulphuric acid, as well as Pellagri's reaction. However, the larger portion of the two, when treated with both

Froehde's reagent and formaldehyd sulphuric acid changed to a green color in a very short time, which true morphin does not. The two portions combined gave a faint reaction for apomorphin, which was to be expected since the residue had been treated with hydrochloric acid. The amount apparently was negligible.

It was very desirable to note the effect of this substance on a normal dog. Accordingly, a solution was made and injected subcutaneously into the one that had recovered completely from the morphin blood mixture. There undoubtedly was more than the equivalent of 4 grains (0.26 gm.) of morphin sulphate remaining after the tests had been made, so it was reasonable to expect signs of morphin poisoning had this been the unchanged drug.

The injection was given at 12:40 p. m., June 26, and aside from vomiting twice, the animal had no symptoms whatever. The dog appeared perfectly normal, and at no time did it show a tendency to develop lethargy and stupor, which is a characteristic effect of morphin. Obviously, this was a substance which, in the main, accorded with morphin so far as the chemical tests were concerned, but which lacked the toxic qualities of the alkaloid. The National Standard Dispensatory (Edition 3) states that the development of a green color with the formaldehyd sulphuric acid test and with Froehde's reagent is the feature which distinguishes pseudomorphin or oxydimorphin from unchanged morphin. It does not state whether this color is produced immediately or whether it develops from the reddish purple, on standing, as in the latter case.

As a further control and to test the susceptibility of this dog to morphin, 130 mg. (2 grains) of morphin sulphate were injected at 9:15 a. m., June 27.

The objective symptoms which developed, within a short time after the injection, consisted of salivation, rapid breathing and lethargy. The dog became stuporous and indisposed to move, the general effect, however, being less than that following the injection of the blood containing 195 mg. (3 grains) of morphin, June 23. While it had recovered almost entirely, June 28, there was sufficient proof that it reacted very definitely to the small dose administered.

CONCLUSIONS

While the work is far from being as complete and convincing as it was expected it would be at the outset, nevertheless, it is believed that certain tentative conclusions are justified.

1. The electrocardiograph does not show the cardiac disturbances which we were led to expect would occur in accordance with Valenti's

observations. While the highest dosage in any one day was less than that administered by Valenti to his animals, the period was much longer and the amount of morphin was either equal to or several times greater than he used, so this could hardly have been a disturbing feature in the experiment.

2. The fact that the immunity developed by increased dosage disappears very rapidly is shown by the fact that two out of three dogs succumbed, and one narrowly escaped, when the accustomed amount of morphin was given after an abstinence of only ten days (July 21-31, 1923). This fact, which we know also holds true for human addicts, argues against the presence of an antibody.

3. Whole blood does not measurably protect a normal animal, even though the blood has been given ample time to alter, combine or destroy the morphin. Apparently, the symptoms are protracted, probably owing to the slower absorption of the protein alkaloid combination.

4. Morphin, unlike quinin, is not abstracted from serum by the red cells. These apparently play no part whatever in protecting the body from the poisonous action. Whether the serum produces any alteration in the morphin molecule, we do not know; that it was not destroyed is shown by the recovery from the serum.

5. Morphin injected into a portal branch passes rapidly into the general circulation and can be obtained from the blood a few minutes after the injection. It is probably altered, because the identification tests, while faint, show a greenish tinge. This is also the case with morphin which remains behind in the liver capillaries and which is recovered by perfusion with distilled water.

6. Liver tissue alters morphin very markedly and the resultant change in the structure is probably similar to that observed by Albanese. Whatever this substance may be, and we are by no means certain that it is entirely pseudomorphin, it is, at any rate, innocuous, and produces no symptoms of morphin poisoning when injected into a susceptible animal.

7. It is highly probable that the liver is at least one of the organs, if not the principal one, involved in the destruction of morphin.

ACTION OF DIGITALIS IN THE PRESENCE OF CORONARY OBSTRUCTION

AN EXPERIMENTAL STUDY *

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The present investigation was undertaken to determine whether interference with the coronary circulation has any effect on the tolerance of an animal to the digitalis bodies.[1]

There has long been a certain hesitation to administer digitalis to patients with heart failure associated with disorders of rhythm similar to those arising from excessive digitalization. Because of the striking similarity between the cardiac disturbances resulting from diphtheria and those from large doses of digitalis, McCullough [2] recommended that the drug be withheld in this disease. The existence of such disorders as premature beats, coupling, various degrees of heart block and pulsus alternans has been taken by some as a contraindication to the use of digitalis, or, at least, as an indication for especial caution in its administration. It has seemed logical to assume that the occurrence of these abnormal phenomena implied a predisposition in the heart to their development through the digitalis bodies that are capable of producing them in the normal heart. But evidence appeared from time to time that challenged this supposition. Bie and Schwensen [3] recorded the effects of digitalis in two patients with diphtheria who had developed a "complex irregularity" of the heart, which was fatal in all of ten patients reported by one of the authors previously. The administration of digitalis in full doses to both patients was followed by the disappearance of the irregularities. One recovered entirely; the other developed further disturbances of rhythm, and died in several days. Bush [4] reported some experiments from which he deduced that diphtheria toxin rendered the heart of the dog and of the frog more susceptible to ouabain, but his data do not warrant his conclusions. Wenckebach [5]

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1. The words "digitalis" and "ouabain" are employed interchangeably in this paper, although only ouabain was used for injection.

2. McCullough, H.: On the Administration of Digitalis to Children with Diphtheria, South. M. J. **14**:110 (Feb.) 1921.

3. Bie, V., and Schwensen, C.: The Effect of Digitalis in Two Cases of Arrhythmia in Diphtheria, J. Infect. Dis. **30**:308 (March) 1922.

4. Bush, A. D.: Drug Action as Modified by Disease Toxins, I, Ouabain Vs. Diphtheria Toxin, J. Pharmacol. & Exper. Therap. **13**:55 (April) 1919.

5. Wenckebach, K. F.: The Effects of Digitalis on the Human Heart, Brit. M. J. **2**:1600, 1910.

observed that troublesome extrasystoles, which had persisted for a long time, disappeared after digitalis medication. Edens and Huber [6] recorded similar observations. While pulsus alternans has been seen in a few cases to follow overdigitalization, digitalis administered to patients with pulsus alternans has sometimes abolished it.[5] Christian [7] observed that, in pulsus alternans, digitalis frequently produced good results, yet he warned that, in view of the great impairment of the myocardium in this condition, the likelihood of improvement was much reduced and to push digitalis in such a case might do much damage. Windle,[8] on the other hand, observed no harm from digitalis in 100 patients with pulsus alternans, though he found that frequently the disparity between the beats was diminished or abolished and that the general symptoms were improved. He recommended the use of digitalis until the onset of vomiting or coupled rhythm.

The discrepancies in clinical reports may be partly explained by the complex nature of digitalis action. For example, small doses stimulate the vagus and diminish the excitability of the heart; large doses may increase the irritability of the heart by direct action on the myocardium. Thus, small doses may abolish extrasystoles; large doses produce them.[5] It also seems more than probable that a certain irregularity of the heart, being symptomatic of widely different conditions, as, for instance, diphtheria, on the one hand, and arteriosclerotic heart failure, on the other, may show as wide variations in response to digitalis. In one instance, it is conceivable that the drug will have no effect or even, in some case, exaggerate the disorder; in another instance, with improvement in the heart action, the irregularity may disappear.

In this connection, Windle [8] has called attention to the fact that alternation of the pulse is less apt to persist in rheumatic hearts than in old arteriosclerotic hearts because of the difference in the circumstances producing the irregularity. In the first case, it occurs generally when an added strain is put on a decompensated heart, but disappears with improvement in the muscle function. In the second instance, it appears generally as evidence of irreparable damage to the myocardium. In view of these and many similar observations, it is evident that theoretic deductions in connection with the effects of digitalis, in various disorders of the cardiac mechanism or in conditions leading to such disorders, are neither justified nor safe. Each condition requires separate investigation.

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6. Edens and Huber: Ueber Digitalis Bigeminie, Deutsch. Arch. f. klin. Med. **118**:476, 1916.

7. Christian, N. A.: The Use of Digitalis in Various Forms of Cardiac Arrhythmia, Boston M. & S. J. **173**:306 (Aug. 26) 1915.

8. Windle, J. D.: Clinical Observations on the Effect of Digitalis in Heart Disease with Pulsus Alternans, Quart. J. Med. **10**:275 (July) 1917.

The alarming symptoms of circulatory failure, often supervening rapidly in patients surviving the immediate effects of coronary obstruction, demand heroic treatment. But especial caution is enjoyed in the administration of digitalis in this condition. Various investigators have shown that the occlusion of coronary vessels in animals gives rise to fibrillation of the ventricles.[9] Digitalis in fatal doses causes ventricular fibrillation almost invariably in the cat, and Reid [10] has reported a similar disturbance with overdigitalization in man. Robinson and Bredeck [11] described a patient of whom the electrocardiogram showed a high degree of intraventricular block preceding an attack of ventricular fibrillation. The administration of 1 mg. of strophanthin, intravenously, caused an increase in the irregular ventricular complexes simulating the condition of "potential fibrillation" of Levy and Lewis.[12] (Necropsy, in this patient, did not reveal any gross interference with the coronary circulation.) Since the occlusion of coronary vessels and digitalis may each give rise to fibrillation of the ventricles, and since a potential fibrillary state may obtain which can be exaggerated by digitalis, the inference is natural that such a state may be produced by coronary obstruction and render digitalis in this condition a dangerous drug. There had been no experimental, and very little clinical, evidence when the present investigation was undertaken which throws any light on this subject.

Experiments were, therefore, performed to show whether obstruction to any particular portion of the coronary circulation alters the susceptibility of the heart to the toxic action of ouabain. If it does not, and if a diminished tolerance to digitalis can be created by ligation, such a state should exist in those animals which survive a degree of interference with the coronary circulation causing spontaneous ventricular fibrillation in a large percentage of them.

METHOD AND EFFECTS OF LIGATION

Over fifty experiments were performed on the cat. This animal is particularly well suited to experimentation with digitalis because of

9. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918. Lewis, T.: The Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, Heart **1**:98, 1909. Miller, J. L., and Matthews, S. A.: Effect on the Heart of Experimental Obstruction of the Left Coronary Artery, Arch. Int. Med. **3**:477 (June) 1909.

10. Reid, W. D.: Ventricular Ectopic Tachycardia Complicating Digitalis, Arch. Int. Med. **33**:23 (Jan.) 1924.

11. Robinson, G. C., and Bredeck, J. F.: Ventricular Fibrillation in Man with Cardiac Recovery, Arch. Int. Med. **20**:725 (Nov.) 1917.

12. Levy, A. G., and Lewis, T.: Irregularities Resulting from Inhalation of Low Percentages of Chloroform Vapor, and Their Relationship to Ventricular Fibrillation, Heart **3**:99, 1911.

its resemblance to man in response to this group of drugs.[13] The thoracic cavity was opened by cutting through four or five cartilages close to the sternum, under ether anesthesia and artificial respiration. The pericardium was incised near the base of the heart, and the necessary coronary vessels dissected free for ligation. The thorax was then closed with interrupted sutures and spontaneous respiration resumed, care being taken to close the wound while the lungs were fully inflated. In some of the experiments, the veins were also included in the ligature; in most of them, the arteries only. Necropsies were performed in all cases to confirm the position of the ligature, and to ascertain any gross pathologic changes in the heart.

Certain observations, made during the course of the work, though not directly concerned with the problem, are of sufficient interest to record. In nearly all experiments, ligation of one of the large branches of the coronaries was followed by dilatation of the heart, most pronounced to the right. The effects on the cardiac rhythm of ligation of any of the large branches mentioned in Table 1 were not uniform. For instance, in one experiment, ligation of the right coronary artery resulted in a very slow rate with a 2:1 block, followed in five minutes by ventricular fibrillation. In another experiment, ligation of the right coronary upset the cardiac mechanism in an entirely different manner; there were extrasystoles and periods of extreme tachycardia, followed in six minutes by fibrillation of the ventricles. In other instances, little or no irregularity was seen after ligation of the right coronary. Similar, inconstant disturbances resulted from ligation of the descending branch of the left coronary and of various combinations of branches of the coronary vessels.

The most constant effects were observed after ligation of the entire left coronary artery at the aorta. There was instant blanching of the left side of the heart, with more or less immobilization of the left ventricle, which progressed until the left ventricle practically ceased beating. At the same time, there was dilatation of the right side of the heart, which became livid and continued to beat rapidly and strongly, passing gradually into ventricular fibrillation.

The fibrillation often failed to involve both ventricles. In some instances, it was limited to the right ventricle from the beginning, no movement being perceptible in the left side of the heart, except along the interventricular groove and in a small area at the apex. In other instances, both ventricles fibrillated for the first minute or two, after which the left ceased to show any movement while the right continued to fibrillate. However, both sides of the heart again fibrillated after the ligature was removed and the heart massaged to introduce blood into

13. Gold, Harry: Digitalis Elimination, Arch. Int. Med. **32**:779 (Nov.) 1923.

the coronary vessels. In another experiment, ligation of the left coronary produced fibrillation of the right ventricle interrupted by periods of regular beats. Considerable massage and compression of the heart failed to abolish these interruptions. With the removal of the ligature and slight massage to force blood into the coronary artery, both ventricles promptly went into fibrillation which persisted until death, nine minutes later.

The absence of fibrillation in that part of the heart deprived of blood was also observed in experiments in which the descending branch of the left coronary alone was ligated.

The occurrence of the foregoing phenomena in some experiments and not in others, also the variability of the effects, are probably dependent, partly at least, on differences in the compensatory circulation. Several observers have recorded partial fibrillation of the heart. Garrey [14] produced partial fibrillation of the ventricles by electrical stimulation under certain conditions. Lewis [15] also noted in dogs that

TABLE 1.—*Incidence of Spontaneous Ventricular Fibrillation Following Varying Degrees of Interference with the Coronary Circulation*

Vessels Ligated	Total No. of Experiments	Ventricular Fibrillation		
		Number	Per Cent.	Time
Descending branch left coronary	16	5	31.2	4 min. - 6¾ hrs.
Descending branch left coronary and circumflex posteriorly	2	0	....	
Circumflex branch left coronary	2	0	....	
Right coronary	7	2	28.5	5 min. - 6 min.
Right coronary and circumflex branch left coronary	1	1	....	38 min.
Descending branch left coronary and right coronary	18	10	55.5	1 min. - 2 hrs.
Left coronary	12	12	100.0	1 min. - 10 min.

the damaged muscle, resulting from occlusion of a coronary vessel, failed to participate in the fibrillation. In accordance with the theory of circus movement, it is possible that ligating a large branch of a coronary vessel produces a considerable area of impaired conduction so as to confine the circus movement to the remaining portion of the heart. Since the capacity for maintaining fibrillation varies directly as the tissue mass,[14] it is readily seen that the tendency for fibrillation to persist in that portion of the heart not deprived of circulation will vary in different experiments depending on the degree of anastomosis between the coronary vessels. As blood is introduced into the coronary vessel by the removal of the ligature and compression of the heart, the large area of block is abolished and the portion of the heart previously excluded begins to participate in the fibrillation. The larger tissue mass now involved, in turn, makes it more possible for the fibrillation to persist.

14. Garrey, W. E.: The Nature of Fibrillary Contraction of the Heart; Its Relation to Tissue Mass and Form, Am. J. Physiol. **33**:397, 1914.
15. Lewis (Footnote 9, second reference).

COMMENT

Table 1 shows the incidence of ventricular fibrillation following varying degrees of interference with the coronary circulation. A large number of animals died during the night of the first or the second day. Since the mode of death was not observed and since factors of infection and shock enter to a greater degree on the second and third days, no deductions are drawn from them except to reckon them among the animals failing to show ventricular fibrillation on the day of ligation. In two experiments, the animals were seen in convulsions, probably from ventricular fibrillation, on the day following the ligations. One of these, in which the descending branch of the left coronary artery was occluded, died immediately after the convulsion; the other, in which the descending branch of the left coronary and the right coronary arteries were ligated, recovered and was injected with ouabain. The percentage of animals showing ventricular fibrillation as a result of coronary ligation given in Table 1 is therefore probably too low, representing only those in which ventricular fibrillation or the convulsion was actually observed.

Of the sixteen experiments in which the descending branch of the left coronary was ligated, five animals, or 31.2 per cent., showed ventricular fibrillation in from four minutes to six and three-fourths hours. In one case, as mentioned above, a convulsion occurred on the second day.

Both animals, in which the descending branch of the left coronary, in addition to the first large descending branch on the posterior surface of the left ventricle, were ligated, recovered without any visible disturbance.

Ligation of the circumflex branch of the left coronary, in two experiments, resulted in no perceptible change in the heart action. Both animals were injected with ouabain on the following day.

The right coronary artery was occluded in seven experiments at one-half centimeter from the aorta. The heart in two animals, or 28.5 per cent., went into ventricular fibrillation in five and six minutes, respectively, after the ligation.

In one experiment, the right coronary and the circumflex branch of the left coronary were ligated, with resulting ventricular fibrillation, in thirty-eight minutes.

Eighteen experiments were performed, in which the right coronary and the descending branch of the left were ligated at the same time. Ventricular fibrillation followed in ten animals, or 55.5 per cent., in from one minute to two hours after ligation.

Tying off the entire left coronary artery at the aorta resulted invariably in ventricular fibrillation in twelve experiments.

Some of the animals in which coronary occlusion was not followed by spontaneous ventricular fibrillation were tested for their tolerance to ouabain. A solution of ouabain, 1: 100,000, freshly prepared, was injected slowly into the femoral vein until death occurred. The results are given in Table 2, expressed as the percentage of the average fatal dose of ouabain for the normal cat, taken as 0.1 mg. per kilogram of body weight. The average fatal dose of ouabain for the seventeen experiments is 102.3 per cent. of the average for normal animals.

In Experiment 11, the animal had a convulsion, presumably from ventricular fibrillation about twenty-two hours after ligation of the descending branch of the left coronary and the right coronary. An

TABLE 2.—*Tolerance to Ouabain of Those Animals in Which Coronary Ligation Was Not Followed by Spontaneous Ventricular Fibrillation* *

	Vessel Ligated	Time Elapsed Between Ligation and Injection	Fatal Dose of Ouabain After Operation in Percentage of Average Fatal Dose for Normal Animals
1.	Descending branch left coronary	1 day	80
2.	Descending branch left coronary	1 day	98
3.	Descending branch left coronary	1 day	175
4.	Descending branch left coronary	1 day	87.2
5.	Descending branch left coronary	3 hours	88
6.	Descending branch left coronary and circumflex posteriorly	4 hours	141
7.	Circumflex branch left coronary	1 day	100
8.	Circumflex branch left coronary	1 day	97.1
9.	Right coronary	1 day	130
10.	Right coronary	1 hour	86
11.	Descending branch left coronary and right coronary	1 day	64
12.	Descending branch left coronary and right coronary	1 day	103
13.	Descending branch left coronary and right coronary	1 hour	104
14.	Descending branch left coronary and right coronary	4 hours	105
15.	Left coronary	10 minutes	110
16.	Left coronary	4 minutes	83.3
17.	Left coronary	4 minutes	87.1
	Average		102.3

* Two experiments are omitted from the table, the animals having died atypically after ouabain injection.

hour and fifty-five minutes after the convulsion, ouabain injection was started, the heart going into ventricular fibrillation when 64 per cent. of the average fatal dose had been injected. This result is an exception to that of the other sixteen experiments. The animal may have been somewhat susceptible to ouabain at the start. An extreme variation above or below the average is occasionally encountered in digitalis testing by the cat method (Experiment 3). In nine instances, in which the ligatures were removed following the production of ventricular fibrillation, the heart recovered a normal beat. But this recovery was only temporary, the heart going back into ventricular fibrillation from thirteen to sixty-eight minutes after recovery. Since, therefore, there is a strong tendency for a recurrence of the ventricular fibrillation even after the ligature is removed, such a recurrence might account for the

small dose of ouabain in the foregoing animal, in which there was recovery following the convulsion and the ligature was not removed.

There still remained, however, the consideration that a narrow margin might obtain preceding ventricular fibrillation produced by coronary occlusion, in which fibrillation could be precipitated by digitalis. The foregoing animal, in which the occlusion of the coronoray produced a convulsion with spontaneous recovery, might conceivably have been in such a state and, hence, required less ouabain to cause death. It was desirable, therefore, to test this possibility.

Reference has already been made to the occurrence of ventricular fibrillation interrupted by periods of regular heart beats in a number of the experiments. But in none were the intermissions sufficiently long to permit of testing the tolerance to ouabain. Reference has also been made to the nine experiments, in all of which recovery of the normal beat after removal of the ligature was followed in varying periods of time by a recurrence of the ventricular fibrillation. The intermissions, in most of the latter experiments, were, however, sufficiently long to permit of the ouabain injection. The left coronary artery was, therefore, ligated at the aorta in three experiments, with resulting ventricular fibrillation in from four to ten minutes. The ligature was then removed, and the heart, after some massage and compression, resumed a regular beat. Ouabain was then injected as in the previous experiments. The results are shown in Experiments 15, 16 and 17 in Table 2, the animals requiring respectively 110, 83.3 and 87.1 per cent. of the normal average fatal dose to cause death. In Experiment 17, after the ligature was removed and the normal beat resumed, a ligature was tied on the right coronary prior to the ouabain injection to add further to any predisposition to ventricular fibrillation which might have already existed. Experiment 13 presented a condition similar to that of Experiment 11 discussed above. The animal had a convulsion, presumably from ventricular fibrillation, one hour and thirty-five minutes after ligatures were tied on the descending branch of the left coronary and the right coronary. Twenty-four minutes after recovery, ouabain was injected, taking thirty minutes for the injection. This animal required 104 per cent. of the average fatal dose for the normal animal to cause death.

That the heart in which large branches of the coronary vessels have been occluded is particularly susceptible to some influences causing ventricular fibrillation appears not only from the fact that many go spontaneously into fibrillation but also from the fact that a slight massage, which is without effect on the normal heart, may readily precipitate fibrillation after the ligature has been applied. Nevertheless, the results of seventeen experiments in Table 2 show that the average

fatal dose of ouabain for the group of animals in which various degrees of interference with the coronary circulation prevailed is practically the same as that for normal animals; that the tolerance to ouabain is not affected by ligation of any particular branch of the coronary vessels nor by even extreme degrees of interference. In the light of the data presented, the conclusion is also inevitable that the heart, which as a result of coronary ligation has gone into ventricular fibrillation with spontaneous recovery and which is almost certain again to lapse into ventricular fibrillation, is not necessarily less tolerant to the toxic action of ouabain than the normal heart.

The general tenor of the objections to the use of digitalis in coronary obstruction in man was expressed by Riesman,[16] who said that when the advisability of giving digitalis came up, in a case of coronary thrombosis, he decided not to give it because, in view of the great damage to the myocardium, "it would not do good and might do harm." Theoretically, one could argue both ways. Various degrees of ventricular immobilization take place depending on the degree of impairment of the coronary circulation. This may be partly a protective mechanism against exhaustion. To increase the force of the heart beat in a state of coronary circulation insufficient for greater work might compromise the chance for recovery. On the other hand, one might say that stimulation might help to tide the heart over a period until sufficient collateral circulation is set up to support it. The latter impression was gained by Miller and Matthews in their animal experiments.[17] They also referred to the fact that German writers recommend digitalis in angina pectoris rather than the nitrites.

Herrick[18] stated that the prejudice against the use of digitalis when the myocardium was weak was only partially grounded in fact. He stressed the great value of this drug in coronary occlusion and suggested that quick results be sought in some cases by intravenous or intramuscular injections. Whether digitalis is of any value in the circulatory failure attending coronary obstruction is, however, not within the scope of this investigation. But to conclude from these experiments that digitalis is entirely without danger in coronary occlusion, in man, is hardly justified without further clinical studies. That a functional state of the myocardium may exist in a diseased heart which calls for particular caution in the administration of digitalis, as shown by Robinson and Bredeck, has already been mentioned. A coronary artery may indeed become occluded in a diseased heart which

16. Riesman, D.: Coronary Thrombosis, M. Clin. N. A. **6**:851 (Jan.) 1923.
17. Miller and Matthews (Footnote 9, third reference).
18. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **69**:2015 (Dec. 7) 1912.

is already the seat of a high degree of intraventricular block, seen by them in the electrocardiogram. I have simply called attention to the fact that it was mainly from indirect experimental evidence that the inference was drawn that, in man, digitalis might precipitate ventricular fibrillation more readily in the presence of coronary obstruction than in the normal heart. The direct experimental data set forth in this paper lend no support to this belief.

SUMMARY AND CONCLUSIONS

1. More than fifty experiments have been performed on the cat to determine whether coronary occlusion changes the tolerance of an animal to the toxic action of the digitalis bodies.

2. Evidence is cited which shows that theoretic generalizations in connection with the response to digitalis in disturbances of the cardiac mechanism, or in conditions leading to such disturbances, are not justified.

3. Effects of occlusion of different parts of the coronary circulation vary widely, depending on the differences in the compensatory circulation. No constantly occurring irregularities were observed after ligation of any particular branch of the coronary vessels.

4. The failure of the portion of the heart deprived of blood to fibrillate is probably due to an area of block confining the circus movement to the remaining portion of the heart. The failure of the fibrillation to persist after ligation of a large coronary vessel is probably due to the diminished tissue mass involved in the fibrillation.

5. A heart that has been in ventricular fibrillation from coronary occlusion and has recovered temporarily also shows no diminished tolerance to the toxic action of digitalis (ouabain).

6. The average fatal dose of digitalis (ouabain) for seventeen animals with varying degrees of coronary obstruction was the same as that for normal animals. The experimental data, therefore, lend no support to the fear that in the presence of coronary occlusion digitalis may precipitate ventricular fibrillation more readily than in the normal heart.

THE EXPERIMENTAL PRODUCTION OF HYPERTENSION *

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Hypertension, chronic nephritis and their related heart conditions are subjects of increasing interest because they are causing more deaths than any other disease process. This may be due, in part, to the prolongation of life. A larger number of persons are thus allowed to enter the decade of life when degenerative cardiovascular and renal conditions are most prone to occur. If the span of life is further increased, as seems likely, degenerative lesions will affect a still larger number of persons.

In spite of the great amount of work that has been done, the cause of high blood pressure and its frequently associated chronic nephritis has not been determined. The clinical importance of this subject warrants continued search for the causes of these conditions.

The rôle of excessive protein metabolism as an etiologic factor in arteriosclerosis and chronic nephritis has long been a matter of debate. There are many students of this question who feel that excessive protein diets are directly responsible for the degenerative vascular-renal diseases. There are others who are equally positive that this theory is wrong. One of the contentions raised against this relationship is that an increase in blood pressure has not been produced experimentally by feeding diets high in protein.

In this preliminary report, we wish to record some of the results of a carefully conducted group of experiments in which the relationship between high protein diets and blood pressure was studied. In three groups of rabbits on high protein diets for twenty-one months, which is the duration of the experiments to date, an increased blood pressure has developed and persisted. In a fourth group of control animals, kept under the same conditions as the others, the diet alone differing, the blood pressure has continued at a normal reading for a rabbit, which is from 70 to 80 mm. of mercury.

The difficulty in obtaining satisfactory blood pressure readings, in experimental animals over long periods of time, is responsible for the small amount of work done along these lines. We have succeeded in

* From the laboratories of the Potter Memorial Clinic and the Santa Barbara Cottage Hospital.

finding only one reported group of experiments in which the blood pressure was followed for a definite period of time. Schmidtmann [1] took blood pressure readings for periods varying from five to nine months. Using a slight modification of the method suggested by von Eweyk and

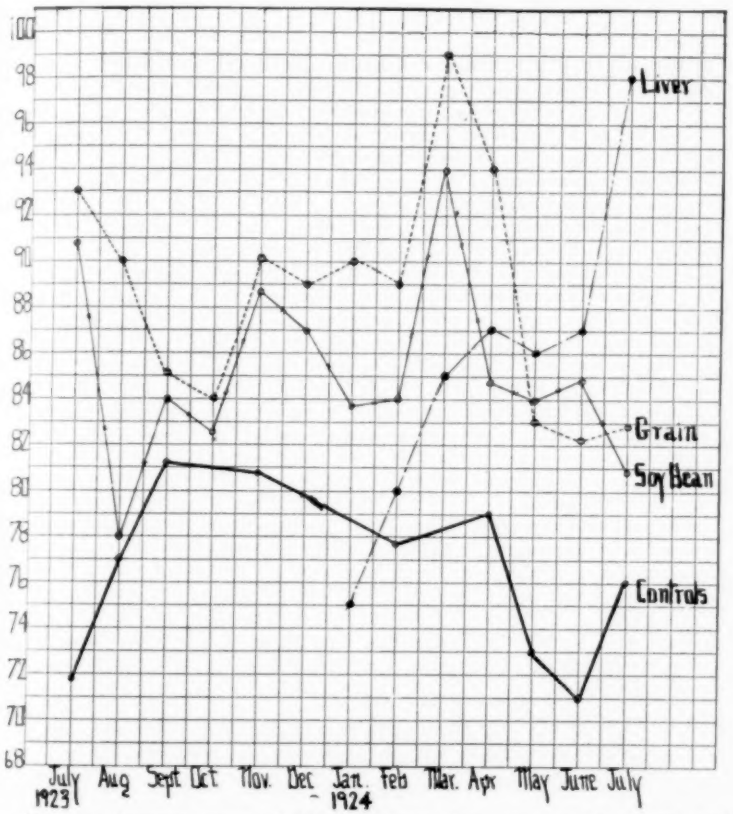

Chart 1.—Average range of blood pressure for one year in control and high protein diet groups of animals.

Schmidtmann,[2] we have taken the blood pressure of our animals one or more times a month for the last twenty-one months.

Two persons are necessary in making these determinations. The rabbit, with a bandage over its eyes, is held in the lap of an assistant.

1. Schmidtmann, M.: Experimentelle Studien zur Pathogenese der Arteriosklerose, Virchows Arch. f. path. Anat. **237**:1, 1922.

2. Van Eweyk, C., and Schmidtmann, M.: Zur Methodik der Blutdruckmessung beim Kaninchen, Virchows Arch. f. path. Anat. **236**:420, 1921.

In this position, it seldom struggles. The blood is compressed from the foreleg by winding a rubber bandage from the toes upward. A small rubber cuff is then placed about the upper part of the leg. The cuff is connected with a mercury manometer (Baumanometer) and inflated to from 140 to 150 mm. of mercury. The compressing bandage is then removed from the lower part of the limb. A pea sized piece of skin is snipped off the front of the leg over the anterior tibial artery. The pressure in the manometer is allowed to drop until the blood is seen to shoot down through the artery, which is exposed through the window in the skin. A second check on this reading is obtained by observing the pressure at which the small capillaries in the skin at the edges of the window begin to ooze. This occurs at about 20 mm. of mercury lower pressure than the reading obtained by noting the sudden filling of the larger artery. Repeated readings may be made through the same window during an afternoon. Following the final reading, the window is painted with iodin, and the animal replaced in its cage. The wound is entirely healed within from seven to ten days. We have had no instances of infection following several thousand blood pressure determinations.

The results of the average of the monthly readings of twelve normal (control) rabbits from July, 1923, to July, 1924, is recorded in Chart 1. It will be noted that the average pressure varied between 72 and 81 mm. of mercury.

A second group of twelve rabbits, whose phenolsulphonephthalein output ranged from 65 to 80 per cent., whose urines contained neither albumin nor casts, whose blood nonprotein nitrogen, urea nitrogen and carbon dioxid were within normal limits, and whose systolic blood pressure ranged between 72 and 78 mm. of mercury over a period of three months, was placed on a diet high in liver protein.

The criticism that has been raised about work done by Newburg and Clarkson [3] and others concerning the production of arteriosclerosis and kidney damage, in feeding experiments, has been that our present knowledge of foods does not permit us to make deductions concerning one factor as protein when other food components are deficient in amount or quality. To avoid this criticism, we used, for this group of animals, a diet originally suggested by McCollum,[4] which contains all the elements essential to growth and maintenance. It consists of: liver, 20 per cent.; casein, 20 per cent.; maize, 20 per cent.; wheat, 30 per cent.; navy beans, 5.5 per cent.; cod liver oil, 2 per cent.; calcium carbonate, 1.5 per cent., and salt, 1 per cent. Six weeks following the

3. Newberg, L. H., and Clarkson, Sarah: Renal Injury Produced in Rabbits by Diets Containing Meat, Arch. Int. Med. **22**:850 (Dec.) 1923.

4. Polvogt, L. M.; McCollum, E. V., and Simmonds, Nina: The Production of Kidney Lesions in Rats by Diets Defective Only in That They Contain Excessive Amounts of Protein, Bull. Johns Hopkins Hosp. **34**:168 (May) 1923.

starting of this diet, the blood pressures of these animals were elevated without exception. This increase in pressure has continued, as is shown in Chart 1. The nonprotein nitrogen and the urea nitrogen of the blood increased in amount, and the urine regularly contained casts and albumin after the sixth week of the experiment (Charts 2 and 3). The reaction of the urines in this group has been acid.

A third group of twelve rabbits, after having been studied so as to exclude any that might have a spontaneous nephritis, was placed on a

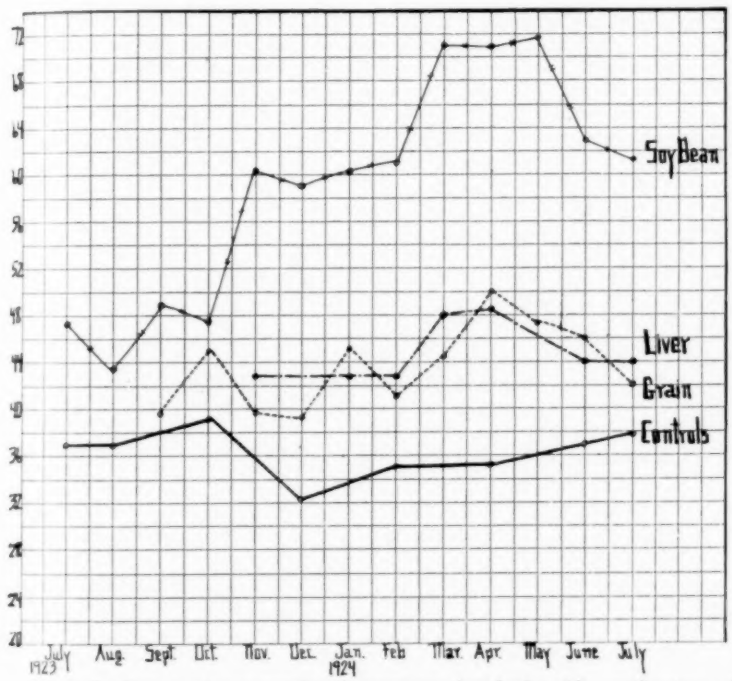

Chart 2.—Range of nonprotein nitrogen per hundred cubic centimeters of blood for period of one year in four groups of animals.

16 per cent. oat protein diet. The bulk of this diet consisted of oats, but cod liver oil and tomato were given ad libitum, and alfalfa was given at intervals to prevent the development of deficiency diseases from lack of vitamins. Six months after this diet was started, the blood pressures were elevated and have continued elevated to the present (twenty-one months). The urine contained albumin and casts by the fourth and the fifth month. The nonprotein nitrogen and urea nitrogen of the blood has increased in amount (Charts 2 and 3). The reaction of the urine is acid.

A fourth group of twelve normal rabbits was placed on a 38 per cent. soy bean protein diet. In addition to the soy beans, cod liver oil, tomato and alfalfa were given, as stated above. Within four months, an elevation of the blood pressure was noted. Albumin was not found regularly in the urine until almost a year after the protein feeding was commenced. An increase in the nonprotein nitrogen and urea nitrogen of the blood was noted in the ninth month. This, too, has continued. The urine of this group has remained alkaline.

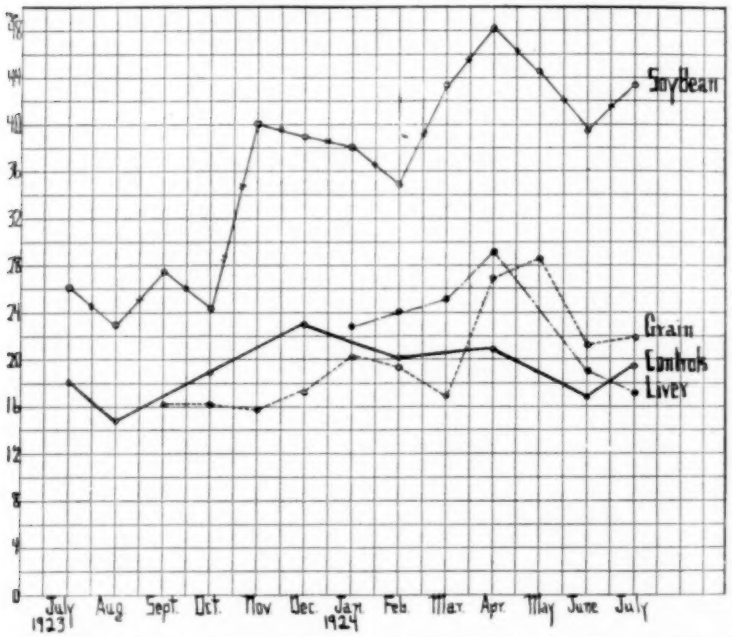

Chart 3.—Range of urea nitrogen per hundred cubic centimeters of blood for period of one year in four groups of animals.

On the completion of these experiments, a careful pathologic study will be made of the kidneys, blood vessels, liver and other viscera. It would seem that marked changes would be found.

COMMENT

The results of our experiments suggest that excessive protein diets will cause an increase in blood pressure. In addition, evidence of disturbed renal function is found by the presence of albumin and casts in the urine, and by the increase of nitrogenous end products, nonprotein nitrogen and urea nitrogen in the blood.

The increase in blood pressure has been most marked in the group of animals on a liver protein diet. The presence of albumin and casts in the urine and the increase in pressure were noted at the sixth week of the experiment, which is earlier than such changes occurred in the other groups. The blood pressures in the group fed on soy bean protein were elevated before changes occurred in the urine or in the blood.

The possibility that acid ash diets necessitating the excretion of highly acid urines over long periods of time might be responsible for the development of high blood pressure and degenerative kidney lesions

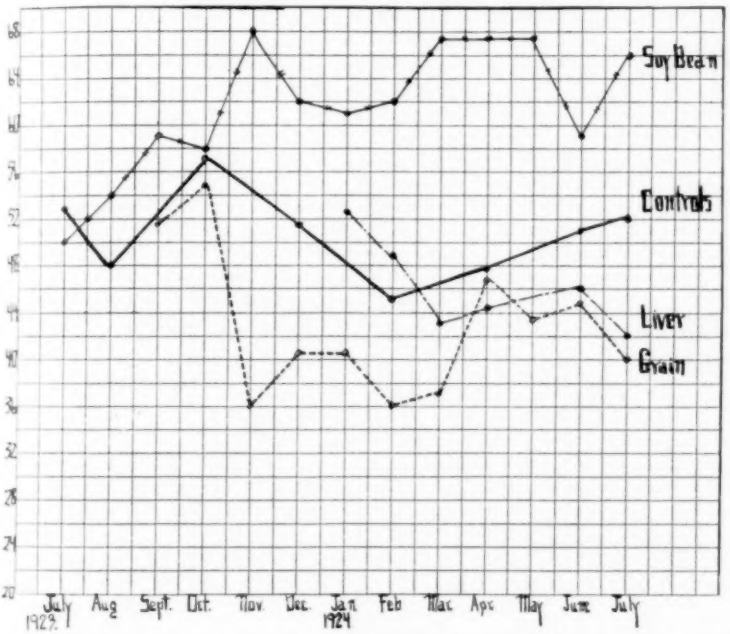

Chart 4.—Range of carbon dioxid capacity of blood plasma for one year in four groups of animals, per cent. by volume.

is a new suggestion. Clinically, there are facts that give weight to this theory. Among these is the unmistakable improvement that occurs in persons with hypertension and chronic nephritis when placed on a basic (alkaline) diet. The oat group of experimental animals have continuously acid urines, due to the acid ash of the oat protein. The soy bean group have shown an elevation of the blood pressure and changes in the blood and urine while the alkaline ash of the soy bean has kept the urines alkaline. The carbon dioxid of the blood serum has remained high in this group, whereas, in the liver and oat protein groups, these

readings have been lower than in the control group. The occurrence of these changes, in the group whose urines are alkaline, does not invalidate the foregoing theory regarding the causation of hypertension and chronic nephritis.

Fisher [5] produced nephritis by the exhibition of excessive alkali. The soy bean diet gives a very alkaline reaction to the urine. The hydrogen ion concentration of these urines ranges from 8.8 to 9. A

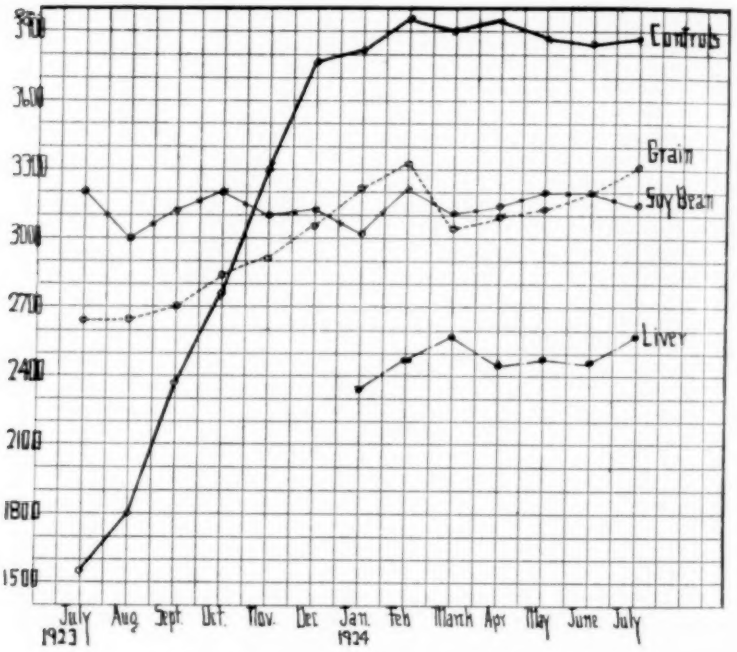

Chart 5.—Increase in weight from July, 1923, to July, 1924.

neutral urine has a p_H of 7. The excessively alkaline ash diet, as evidenced by the excretion of an abnormally alkaline urine for many months, might well be responsible for the changes that we have noted.

The weight curves (Chart 5) indicate a graduate increase in all groups of animals. The controls are now the largest animals. The soy bean group still appear in good condition. The fur of the oat and liver groups has become dry, and these animals are not so robust.

5. Fisher, Martin: Edema and Nephritis, New York, John Wiley & Sons, p. 428.

We are giving special attention to particular metabolites of the nonprotein nitrogen group to see if an increase of the amino acids or of guanidin is present. Major [6] has recently called attention to the pressor effect of guanidin bases.

SUMMARY

Three groups of rabbits placed on high protein diets, each group on a different type of protein, developed an increased blood pressure.

Evidence of renal irritation was offered by the appearance and persistence of albumin and casts in the urines of these animals, and by a retention of nonprotein nitrogen and urea nitrogen in the blood. There also was evidence of acidosis, as shown by a continued decrease in the carbon dioxid of the blood plasma of the oat and liver protein groups of animals. This decrease in the carbon dioxid was not present in the soy bean group, whose urines were alkaline.

It is suggested that diets containing an excessive acid or alkaline ash, necessitating the excretion of excessively acid or alkaline urines over long periods of time, might, in themselves, be responsible for degenerative blood vessel and kidney changes.

6. Major, R. H.: Relationship Between Certain Products of Metabolism and Hypertension, J. A. M. A. **83**:81 (July 12) 1924.

THE EFFECT OF INGESTION OF YEAST ON THE LEUKOCYTE COUNT *

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When a foreign protein is injected into the blood stream, it has been observed that the number of leukocytes is at first usually diminished, later markedly increased and that finally there is a gradual decrease, the number of leukocytes falling to approximately the original level. It also has been observed that during the height of digestion and absorption in the small intestine, the leukocytes are increased in number.

In connection with a study on the effect of ingestion of yeast in certain pathologic conditions, we were interested in a consideration of the mechanism of its action. In cases of infection, it is generally assumed that an increase in the number of leukocytes indicates a satisfactory response on the part of the organism in defending itself against the invading bacteria. There are, however, numerous investigators who do not believe that an increase in the leukocyte count necessarily accompanies such a defensive response. It has been observed that no improvement occurred with marked leukocytosis, and that marked improvement may occur without leukocytosis.

The ingestion of yeast has been assumed to produce a leukocytosis. Failing to find any literature on this subject, we undertook experiments to study the effect of the ingestion of yeast on the leukocyte count.

EXPERIMENTS

For the purpose of such experiments, we appealed for volunteers to the members of the present first and second year classes in the University of Illinois College of Medicine. Twenty-two members of these two classes volunteered and thus made this work possible. The method of procedure was as follows:

The blood samples were taken at 9:30 a. m. on eight successive mornings. All these subjects were requested to attempt to maintain a reasonable uniformity in their diets and physical activities. The morning meal was supposed to have been ingested at approximately the same period of time before the taking of the blood sample. The leukocyte count was made as follows:

A standard white pipet and Thoma-Zeiss hemocytometer were used in this work. The first drop of blood was wiped away and the second

* From the University Hospital and the Laboratory of Physiological Chemistry, University of Illinois College of Medicine.

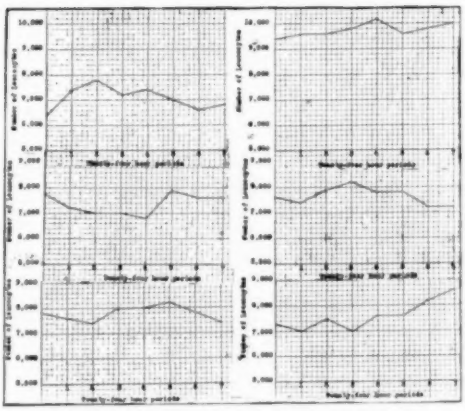

Chart 1.—Curves showing normal variations

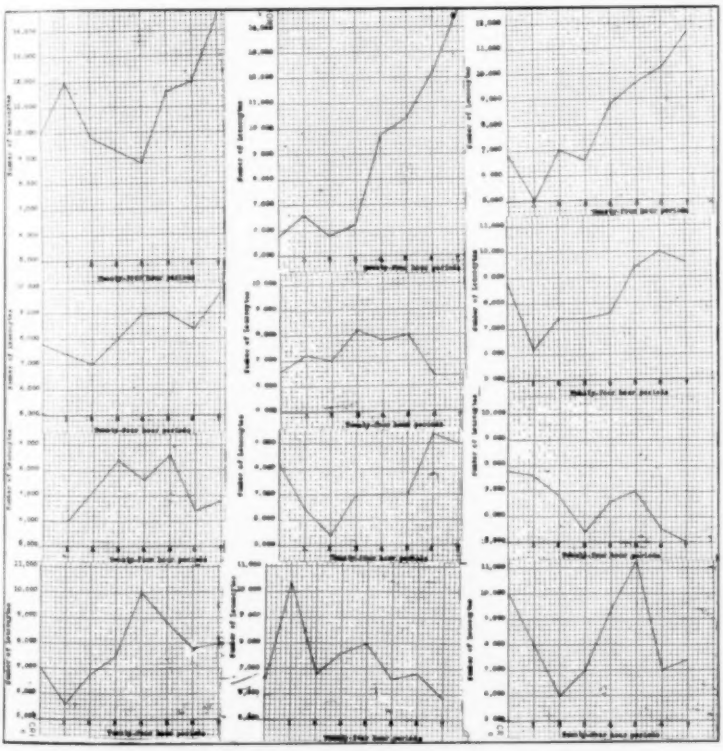

Chart 2.—Curves showing effect of ingestion of yeast on leukocyte count.

drop drawn to the 0.5 mark. The blood was diluted one-twentieth with 1 per cent. acetic acid, and the average count of 5 large squares (1 sq. mm.) taken. This was multiplied by 200 to give the normal count in one cubic millimeter.

Six of the ten subjects that we studied with a view to establishing a base line showed a small amount of variation from day to day. Three of the remaining four developed mild respiratory infections. At the time the symptoms became noticeable, there was a marked increase in the leukocyte count. The tenth subject showed a decided rise in the leukocyte count, during the latter part of the period, without our being able to arrive at any explanation. The six curves (Chart 1) furnish a base line for comparison with the curves obtained from the subjects who were given yeast. The maximum variation obtained in these six curves is 1,600.

The subjects who aided us in the study of the effect of yeast reported, the first day, without any yeast ingestion; after the blood count was taken, they ingested three cakes of one of the common market varieties of fresh yeast (Fleischmann) per day—one cake between breakfast and lunch, one cake between lunch and dinner, and one cake between dinner and the time of retiring. This was continued for seven days. The subjects were carefully watched for infections or other conditions which might alter the count. No such infections or conditions were observed. Our results are shown in Chart 2. In some cases there is no initial diminution in the leukocyte count. Possibly, the interval of twenty-four hours between the first and the second counts was sufficiently long so that the decrease had disappeared and increase had begun. Some of the cases did not show a marked increase in the number of leukocytes. However, the majority of these cases studied showed a definite increase in the leukocyte count, which was much greater than the normal variation under the conditions of our experiment.

We are indebted to Drs. Brooke and Lorfeld for the technical assistance in this work.

SUMMARY

On the basis of these results we conclude that in most cases the ingestion of three cakes of yeast daily causes a marked increase in the leukocyte count in apparently normal persons.

MERCUROCHROME-220 SOLUBLE AS A BILIARY ANTISEPTIC

AN EXPERIMENTAL STUDY *

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AND
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Although there have been many experimental and clinical attempts to find a biliary antiseptic,[1] so far no drug has been shown to have a sufficiently strong or constant therapeutic action in bile to afford a solution of this important problem. Surgical intervention, which hitherto has been the most satisfactory method of treatment, theoretically is not the method of choice. Aside from its own difficulties, it often fails to eliminate the infection, especially in cases in which the bile passages and liver are involved.[2] Moreover, even in cases of cholelithiasis requiring surgical treatment, it would be of great value to control an accompanying infection before operation. If, therefore, a drug can be found which can be shown to be excreted by the liver, to be present in the bile in bacteriostatic or bactericidal strength, and to be of low enough toxicity to allow its safe clinical use, it would be of great value in the treatment of biliary infections. The use of such a drug would be indicated not only in the treatment of active infections, in which both the alleviation of the immediate condition and the relation between infection and cholelithiasis [3] are important, but also in the treatment of infections of the latent or chronic type, especially as found in bacterial carriers.

A variety of organisms must be considered in the study of biliary antisepsis. Of these, *Eberthella typhi* (*B. typhosus*) has been the most thoroughly studied.[4] *Salmonella paratyphi* (*B. paratyphosus A*), *Salmonella schotmülleri* (*B. paratyphosus B*), the colon group bacilli, *Eberthella paradysenteriae* (*Hiss*) and (*Flexner*) and vibrio comma, and the staphylococci [5] should be considered.

A résumé of the numerous previous attempts to find a biliary antiseptic of value against one or more of these organisms shows the lack of success in this search so far, and indicates clearly the value of studying mercurochrome-220 soluble from this point of view. This study is also suggested because, since the original presentation of mercurochrome-220 as a local germicide,[6] the possibility of its use intravenously and also of its administration by mouth has been shown.[8] Working simultaneously

* From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital.

with us, Rosenthal and White [9] have shown that mercurochome is eliminated through the bile. They say:

> Mercurochrome departs from the blood more rapidly than flumerin, and is excreted in the bile in larger quantities. Thus in two rabbits there was an average biliary excretion of 25 per cent. in one hour and 44 per cent. in the two hours after injection.

Our own experiments on the excretion of mercurochrome in bile are shown in Tables 1 and 2. The method employed consisted of ligating the common duct of a rabbit, under ether anesthesia, and inserting a drainage tube into the fundus of the gallbladder. Through this drainage tube, specimens of bile were collected, a control specimen before drug administration always being obtained. The appearance time of the drug was noted. As the readings of drug concentrations in bile are difficult, after approximate whole bile observations, the bile pigments were dissolved by the addition of an equal part of Schlessinger's solution (10 per cent. solution of zinc acetate in alcohol) to each specimen. After allowing the sediment to settle, direct readings could be made against standard mercurochrome dilutions. These tests proved to be of value, for in highly colored bile the presence of the drug was revealed in this way, when otherwise it would have been impossible to detect it.

These tables show that the drug first appears in the bile about fifteen minutes after an intravenous injection of 5 mg. per kilogram of body weight; that it is present in its strongest concentration, from 1:5,000 to 1:25,000, the first two hours after injection; that it continues to be excreted in a concentration of from 1:8,000 to 1:50,000 the next two hours, and that it has been entirely eliminated in twenty-four hours. That is, by intravenous administration, mercurochrome reaches the bile quickly, is present in strong concentration for at least four hours, and is gone in twenty-four hours. Giving the drug by stomach, however, results in its appearance in the bile much more slowly —approximately the second hour after administration—and in concentrations weaker than those obtained by intravenous injection but still of bacteriostatic or bactericidal strength, as will be shown later. By properly adjusting the dosage of drug administered by mouth, it should be possible to obtain a constant presence of drug in the bile, which could be continued for at least a week, as Young, Scott and Hill [8] have shown that 900 mg. a day of mercurochrome by mouth may be given clinically for a week or more without injury. In these experiments, therefore, the first requirement for a biliary antiseptic has been met, namely, it has been shown that mercurochrome-220, given intravenously or by mouth, is excreted through the bile in strong concentrations.

In studying the germicidal action of mercurochrome in bile, three methods have been used: first, entirely in vitro tests in bile; second,

combined in vivo-in vitro tests, in which the germicidal action of bile after the administration of mercurochrome was tested; and third,

TABLE 1.—*Appearance Time and Approximate Concentration of Mercurochrome-220 in Gallbladder Bile After Intravenous Infection of 5 Mg. Per Kilogram to Rabbits*

	Rabbit A		Rabbit B	
Time	Whole Bile Readings	Pigment-Free Readings	Whole Bile Readings	Pigment-Free Readings
1. Before injection, control....	No drug	0	No drug	0
2. 0 to 15 minutes after drug...	13 minutes, color change; 14 minutes, definite drug	0	No definite drug	0
3. 16 to 30 minutes after drug..	Drug increasingly strong, very heavy by 27 minutes	.....	Sixteenth minute, trace; eighteenth minute, drug present; eighteenth to thirtieth minute, increasingly strong	1:6,000
4. 31 to 45 minutes after drug..	Drug strong throughout	1:5,000	Drug strong throughout	1:5,000
5. 46 to 60 minutes after drug..	Drug strong throughout	1:5,000	Drug strong	1:5,000
6. 1 to 1¼ hours after drug....	Drug very strong	1:7,000	Drug strong	1:6,000
7. 1¼ to 1½ hours after drug..	Drug very strong	1:7,000	Drug strong	1:6,000
8. 1½ to 1¾ hours after drug..	Drug strong	1:25,000	Drug strong	1:6,000
9. 1¾ to 2 hours after drug....	Drug strong	1:25,000	Drug strong	1:6,000
10. 2 to 2¼ hours after drug....	Drug strong	1:20,000	Drug strong	1:8,000
11. 2¼ to 2½ hours after drug..	Drug strong	1:25,000	Drug strong	1:8,000
12. 2½ to 2¾ hours after drug..	Drug strong	1:30,000	Drug strong but less	1:10,000
13. 2¾ to 3 hours after drug....	Drug strong	1:30,000	Drug strong	1:15,000
14. 3 to 3¼ hours after drug....	Drug present	1:35,000	Drug strong	1:20,000
15. 3¼ to 3½ hours after drug..	Drug present	1:40,000	Drug strong	1:20,000
16. 3½ to 3¾ hours after drug..	Drug present	1:40,000	Drug present	1:30,000
17. 3¾ to 4 hours after drug....	Drug present	1:50,000	Drug present	.....
18. 24 hours after injection (15 minute specimen)	No drug	0	No drug	0

TABLE 2.—*Appearance Time and Approximate Concentration of Mercurochrome-220 in Gallbladder Bile of Rabbits After Mercurocrome-220 by Mouth*

	Rabbit A 1 Dose of 50 Mg. per Kg.		Rabbit B 2 Doses of 50 Mg. 4 Hrs. Apart	
Time	Whole Bile Readings	Pigment-Free Readings	Whole Bile Readings	Pigment-Free Readings
Before treatment.....	No drug	0	No drug	0
First hour after dose.....	Very slight trace, bile dark	1:100,000	No visible drug, bile dark	0
Second hour after dose.....	Drug present	1:25,000	Drug present	1:25,000
Third hour after dose.....	Drug present	1:50,000	Drug present	1:50,000
Fourth hour after dose.....	Drug present	1:50,000	Drug present	1:100,000
			Second Dose, 50 mg.	
Fifth hour after dose.....	Drug present	1:55,000	Drug present	1:50,000
Sixth hour after dose.....	Drug present	.....	Drug strong	1:25,000
Seventh hour after first dose....	.....	.....	Drug strong	1:20,000
Eighth hour after first dose....	.....	.....	Drug present	1:50,000
24 hours after first dose.....	.....	.....	No visible drug	1:100,000

entirely in vivo tests, that is, the action of the drug intravenously and by mouth on rabbit gallbladder infections with *Eberthella typhi*. These groups of tests will be discussed separately.

IN VITRO TESTS

In all these, the method of Beckwith [10] was used because it was found to be very satisfactory, and because we desired to have our results as comparable to his as possible. For this reason, through the kindness of Dr. Beckwith, a culture of *B. typhosus* 3 was obtained. As the action of mercurochrome in salt solution and serum had been studied previously,[11] we limited our tests to ox bile, freshly sterilized by autoclaving for twenty minutes at 15 pounds (6.8 kg.) pressure.

The essentials of the method, the exact details of which may be found in Beckwith's article,[10] are as follows: Small agglutination tubes carefully cleaned and sterilized were used, each tube receiving 0.9 c.c. of bile, except the bile control tubes, which received 1 c.c. Dilutions were made by adding 0.1 c.c. of mercurochrome-220 dilution in bile, ten times the finally desired concentration of drug, to 0.9 c.c. of bile. Preliminary tests were done with the dilutions used by Beckwith, that is, 1:1,000, 1:10,000, 1:100,000, and 1:1,000,000; but, as the zones of action were more clearly defined, finally dilutions of 1:1,000, 1:5,000, 1:10,000, 1:25,000, 1:50,000, 1:75,000, 1:100,000 and 1:250,000 were used. In Table 3, in which the results of these tests are given, the killing strength indicates failure to kill at the next dilution in the series just enumerated. Having made and carefully mixed these dilutions of mercurochrome in bile, each tube was inoculated with two loopfuls of a twenty to twenty-four hour broth culture of the test organism, using 0.4 mm. platinum wire with an oese 2 mm. in diameter. Immediately after inoculation, plates were streaked with one loopful of the mixture to control the experiment, and subsequent transfers were made one, two, five and twenty-four hours after inoculation. Parallel series of transfers were also made to broth, as the plate method was found to offer difficulties in certain drug concentrations in which inhibitive amounts of drug were carried over to the agar. In every series the greatest care was taken to inoculate control tubes in drug-free bile with every organism, for the possible bactericidal action of bile has long been noted, especially by Leubuscher,[12] Neufeldt,[13] Talma,[14] Braun,[15] Fornet,[16] Meyerstein,[17] Pies,[18] Nichols,[19] and Beckwith and Lyon.[20] The results of these in vitro tests (Table 3) show that, in bile, mercurochrome in a concentration of 1:1,000 kills all the organisms tested, with the exception of *Staphylococcus aureus*, in one hour, and that in a concentration of 1:5,000 it kills *B. typhosus* 3 in the same length of time. In five hours, with the exception of *Salmonella paratyphi* (*B. paratyphosus A*), *Vibrio comma* and *Staphylococcus aureus*, all organisms were killed in a concentration of 1:25,000, while the twenty-four hour killing strength, excepting *Staphylococcus aureus*, varied from 1:50,000 to 1:100,000. Although too close a comparison cannot be made between different tests,

by comparing these figures with concentrations of mercurochrome found in bile after administration to rabbits, it will be seen that germicidal action in vivo could be expected.

TABLE 3.—*Action of Mercurochrome-220 in Bile in Vitro*

Organism	Drug Concentration Killing in One Hour	Drug Concentration Killing in Two Hours	Drug Concentration Killing in Five Hours	Drug Concentration Killing in Twenty-Four Hours	Drug-Free Bile Control
Eberthella typhi B (Beckwith) (B. typhosus)	1:5,000	1:5,000	1:25,000	1:50,000	Good growth 24 hours
Eberthella typhi (Rawlings)	1:1,000	1:5,000	1:25,000	1:75,000	Good growth 24 hours
Salmonella paratyphi (Paratyphi A)	1:1,000	1:5,000	1:10,000	1:100,000	Good growth 24 hours
Salmonella schotmulleri (Paratyphi B)	1:1,000	1:5,000	1:25,000	1:100,000	Good growth 24 hours
Eberthella paradysenteriae Flexner (B. dysenteriae Flexner)	1:1,000	1:5,000	1:25,000	Bile control bactericidal repeatedly	Good growth through 5 hour tests
Eberthella dysenteriae-shiga	1:1,000	1:1,000	1:25,000	Bile control bactericidal repeatedly	Good growth through 5 hour tests
Escherichia communior (B. coli)	1:1,000	1:1,000	1:25,000	1:75,000	Good growth 24 hours
Vibrio comma	1:1,000	1:5,000	1:10,000	1:50,000	Good growth 24 hours
Staphylococcus aureus	1:100	1:100	1:1,000	1:5,000	Good growth 24 hours

IN VIVO-IN VITRO TESTS

In vivo-in vitro tests, specimens of bile taken from rabbits before and after the administration of mercurochrome were inoculated with *B. typhosus* and tested as in the entirely in vitro tests, that is, one loopful removed just after inoculation and at intervals thereafter, plated and put in broth.

EXPERIMENT 1.—The rabbit had the common duct ligated and the drainage tube inserted in the gallbladder, and, after recovery from the ether anesthesia, was given 5 mg. per kilogram of body weight of mercurochrome, intravenously, specimens of bile being taken before drug administration, and for four hours after injection. There was a delay in appearance of the drug in the bile, until forty-five minutes after injection, which was found to be due to the position of the animal.

TABLE 4.—*Results in Experiment 1*

Specimen	Before Inoculation, Bile Sterility Control	Organisms One Minute after Inoculation	Organisms One Hour after Inoculation	Organisms Twenty-Four Hours after Inoculation
Normal (before drug)	Sterile	Heavy	Heavy	Heavy
First hour after drug (appearance time 45 minutes)	Sterile	Heavy	Heavy	Heavy
Second hour after drug	Sterile	Heavy	Heavy	Sterile
Third hour after drug	Sterile	Heavy	Heavy	Sterile
Fourth hour after drug	Sterile	Heavy	Heavy	Sterile

In this experiment, the bile before drug administration allowing a heavy growth of *Eberthella typhi* twenty-four hours after inoculation, the specimens taken two, three and four hours after drug administration killed the organisms in twenty-four hours.

EXPERIMENT 2.—This experiment was done by one of us (J. H. H.) with Rosenthal,[9] and was prepared first for this paper. A rabbit was given 5 mg. per kilogram of body weight of mercurochrome intravenously, and bile specimens were taken before administration and thirty minutes, one hour and two hours after administration, 2 c.c. of each specimen being inoculated with 0.1 c.c. of a twenty-four hour broth culture of *B. typhosus* 3 and transfer made to agar at once after inoculation, and one, sixteen and twenty-four hours after inoculation.

TABLE 5.—*Results in Experiment 2*

Specimen	Before Inoculation, Bile Sterility Control	Organisms One Minute after Inoculation	Organisms One Hour after Inoculation	Organisms Sixteen Hours after Inoculation	Organisms Twenty-Four Hours after Inoculation
Normal 1 (before drug).....	Three colonies Staphylococcus albus	Heavy Eberthella and one colony Staphylococcus	Heavy Eberthella and two colonies Staphylococcus	Heavy, both organisms	Heavy, both organisms
Normal 2 (before drug).....	Moderate growth Staphylococcus albus	Heavy Eberthella two colonies Staphylococcus	Heavy, both organisms	Heavy, both organisms	Heavy, both organisms
Thirty minutes after drug.....	Moderate growth Staphylococcus albus	Heavy	Sterile	Sterile	Sterile
One hour after drug.....	Two colonies Staphylococcus albus	Heavy	Sterile	Sterile	Sterile
Two hours after drug.....	Three colonies Staphylococcus albus	Heavy; one colony Staphylococcus	Sterile	Sterile	Sterile

In this case, with the control or drug-free specimens allowing a heavy growth of the inoculum, *Eberthella typhi*, and no diminution of the contaminating *Staphylococcus albus* within thirty minutes after drug administration, the bile had become sufficiently bactericidal to kill the large number of organisms inoculated, as well as the staphylococcus, in one hour. Better bactericidal action than this we believe it would be difficult to demonstrate.

IN VIVO TESTS

As Beckwith has shown, especially with the flavines, that drugs active in bile in vitro may not be of use in eliminating biliary infections, we have tested the action of mercurochrome on rabbits with gallbladder infections of *B. typhosus* 3. The infections were obtained by intravenous inoculations, or, more satisfactorily, by direct inoculation of the gallbladder. Even when using the latter method, we felt that it was necessary to control the experiments in two ways, first, by obtaining a positive culture from the bile before treatment and, second, by examining a series of untreated rabbits which had received the same inoculation. The protocols of the experiments are given in Table 6.

From this table, it will be seen that after single intravenous injections of 3 and 5 mg. per kilogram of body weight no organisms could be recovered from the bile of animals in which the infection had been

TABLE 6.—*Treatment of Typhoid Carrier Rabbits with Mercurochrome-220*

Rabbit	Pretreatment Period		Treatment Period		Posttreatment Period	
	Day	Findings	Day	Dose	Day	Findings
1	1	Laparotomy; inoculation of gallbladder with Eberthella typhi (0.5 c.c. of 24 hour broth culture)	16	5 mg. per kilogram intravenously	46	Killed; culture of bile, gallbladder wall, spleen, urine and heart blood sterile
			22	5 mg. per kilogram intravenously		
			25	5 mg. per kilogram intravenously		
	15	Laparotomy; aspiration of gallbladder bile, which showed pure culture of Eberthella typhi	29	5 mg. per kilogram intravenously		
			32	5 mg. per kilogram intravenously		
			36	5 mg. per kilogram intravenously		
			39	5 mg. per kilogram intravenously		
2	1	Intravenous inoculation with 2 c.c. of emulsion of Eberthella typhi culture	20	3 mg. per kilogram intravenously	35	Killed; culture of bile, gallbladder wall, spleen, urine and heart blood sterile; and gallbladder deeply embedded in gallbladder wall greatly thickened liver
	8	Laparotomy; aspiration of gallbladder bile, which was sterile by culture; gallbladder inoculated with 0.1 c.c. of broth culture of Eberthella typhi				
	16	Laparotomy; aspiration of gallbladder bile, which showed pure culture of Eberthella typhi				
3	1	Intravenous inoculation with 2 c.c. of emulsion of Eberthella typhi culture	20	5 mg. per kilogram intravenously	35	Killed; culture of bile, gallbladder wall, spleen, urine and heart blood sterile; gallbladder wall thickened
	8	Laparotomy; aspiration of gallbladder bile, which was sterile by culture; gallbladder inoculated with 0.1 c.c. of broth culture of Eberthella typhi				
	16	Laparotomy; aspiration of gallbladder bile, which showed pure culture of Eberthella typhi				
4	1	Intravenous inoculation with 2 c.c. of emulsion of Eberthella typhi culture	20	Two doses of 7.5 mg. per kilogram each by stomach tube	30	Killed; culture of bile, galbladder wall, spleen, urine and heart blood sterile; gallbladder wall thickened
	8	Laparotomy; aspiration of gallbladder bile, which showed pure culture of Eberthella typhi	21	Two doses as above		
			22	Two doses as above		
			24	Two doses as above		
			25	Two doses as above		
			26	Two doses as above		
			27	Two doses as above (Loss of appetite first 24 hours, after which no abnormality noted)		
5	1	Intravenous inoculation with 2 c.c. of emulsion of Eberthella typhi	..	Untreated control	35	Killed; bile milky with pus; culture of bile heavy growth of Eberthella typhi only
	8	Laparotomy; aspiration of gallbladder bile, which was sterile by culture; inoculation with 0.1 c.c. of broth culture of Eberthella typhi				
6	1	Laparotomy; inoculation of gallbladder with 0.1 c.c. of broth culture of Eberthella typhi	..	Untreated control	33	Killed; large liver abscess, gallbladder thickened and bile purulent; Eberthella typhi in pure culture
7	1	Laparotomy; inoculation of gallbladder with 0.1 c.c. of broth culture of Eberthella typhi	..	Untreated control	33	Killed; gallbladder wall thickened; bile purulent; Eberthella typhi in pure culture
8	1	Laparotomy; inoculation of gallbladder with 0.1 c.c. of broth culture of Eberthella typhi	..	Untreated control	33	Killed; bloody diarrhea; gallbladder thickened, bile purulent; Eberthella typhi in pure culture

demonstrated previously by culture of the bile. Similarly, no organisms were found after repeated intravenous injections of 5 mg. per kilogram of body weight. The bile was found to be sterile after administration of a total of fourteen doses of the drug (two doses daily of 7.5 mg. per kilogram) by mouth. The controls, on the contrary, were positive in every case, the gallbladders of these animals also showing macroscopic evidence of persisting infection.

SUMMARY

It has been shown that mercurochrome is excreted by the liver, that it appears in the bile in strong concentrations, that bile after the intravenous administration of the drug is bactericidal when inoculated with the typhoid bacillus *Eberthella typhi*.

It has also been shown that, in vitro, mercurochrome is active against organisms of the colon-typhoid-dysentery groups and against *Vibrio comma*.

It has been possible to cure rabbits that had been made gallbladder carriers of *Eberthella typhi* by giving mercurochrome intravenously or by mouth.

CONCLUSION

In mercurochrome-220, a drug has been found which experimentally meets the requirements of a biliary antiseptic, in that it is excreted in the bile in bacteriostatic and bactericidal strength, and which, as has been previously shown, is of low enough toxicity to allow its safe clinical use intravenously or by mouth. The trial of mercurochrome clinically in both latent and acute gallbladder infections is not only justified but also clearly indicated from these experimental findings.

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BLOOD VOLUME

I. A METHOD FOR DETERMINING WHOLE BLOOD VOLUME BASED ON THE CIRCULATING CORPUSCLE VOLUME *

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A method is presented for determining whole blood volume by means of the circulating corpuscle volume. After a transfusion of unlike group blood, the transfused corpuscles can be separated from the recipient's corpuscles by agglutinating the latter with a serum of the same type as that of the blood transfused. If the transfusion is of blood of Group 1 (Group 4, Moss) into a recipient of Group 2, 3 or 4 (Group 1, Moss), the separation will be nearly quantitative. Since the amount of blood transfused is known, the degree of its dilution in the recipient may be determined and the blood volume calculated.

The method, which has already been noted,[1] is of interest because, owing to the simplicity of the procedure and to the stability of the unlike group blood in the circulation of the recipient, multiple determinations can be made over a considerable length of time. The method is a by-product of a purely therapeutic measure and inconveniences patients very little. In fact, the procedure is so simple that it would be feasible to run several daily blood volume determinations over a period of two or more weeks. Although the method, dependent as it is on corpuscle counting, does not have the degree of consistency of the dye method,[2] for instance, and is not preferred when that can be used, it nevertheless has the advantage that, since it affords an almost continuous picture of blood volume changes, the possibilities of blood volume behavior may be deduced from it, the verity of which may be checked at appropriate periods by some method mechanically more accurate. In other words, it may be used as a scouting measure, and on apparent blood volume changes of significance the finding can be substantiated by some other procedure, such as injection of vital red. It also has a certain theoretical interest in connection with the question of the equality of distribution of the corpuscles throughout the circulation. The error inherent to the technic is equivalent to that of the routine red cell count.

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The method, which bears certain resemblances to that of Todd,[3] is as follows: A count of the cells in the blood to be transfused is made and the initial unagglutinability of the recipient's blood with Group 1 serum is tested by a method previously described;[4] then the patient, who must be either in Group 2, 3 or 4 (Group 1, Moss) receives a transfusion of 500 c.c., or more, of Group 1 (Group 4, Moss) blood. At any time within two or more weeks, if there does not appear to have been any elimination of the transfused blood, a count of the unagglutinable corpuscles in the patient's venous blood may be made, and from the degree of dilution of the transfused blood in the circulation of the recipient, the volume of the whole blood may be calculated using the formula, $V = \frac{C_t \times V_t}{U_2 - U_1}$, V being the total volume, V_t the volume of the blood transfused, C_t the count of the corpuscles in the blood transfused, and U_1 and U_2 the counts of unagglutinated corpuscles before and after transfusion. For obtaining the venous blood a small syringe containing a trace of dry citrate and fitted with a fine needle may be used without annoying the patient much more than would the ordinary ear puncture. One cubic centimeter of blood or less is sufficient.

The method is of theoretic interest because by means of it a whole blood volume may be derived, which depends on a corpuscle volume measurement; and also because this corpuscle volume measurement does not involve the noncirculating hemoglobin-like substance, as may occur with the carbon monoxid method. The whole blood volume derived from it should correspond to blood volumes obtained by the injection of a plasma soluble substance, except that the error due to irregularities in the relative distribution of plasma and corpuscles should, with this method, be exactly the converse of that involving the use of a serum soluble substance. That this method is based on a direct corpuscle volume determination appears readily on analysis.

It is assumed that the transfused blood corpuscles, $C_t \times V_t$, are evenly mixed with the circulating corpuscles of the recipient, but not necessarily evenly distributed throughout the circulation. Any sample of blood drawn should show the same ratio between the count of the transfused blood corpuscles and the red cell count as exists between the total number of cells injected and the total number of cells in the body. Therefore, $C_t \times V_t$, the number of cells transfused, divided by

3. Todd, C., and White, R. G.: On the Fate of the Red Blood Corpuscles When Injected Into the Circulation of an Animal of the Same Species; with a New Method for the Determination of the Total Volume of the Blood, Proc. Roy. Soc., London **84**:255-259, 1911-1912.

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$U_2 - U_1$, the number of the transfused corpuscles per unit volume of the recipient's blood, multiplied by C, the red cell count for a unit volume of the recipient's blood, determined from the same specimen as U_2, gives the total number of corpuscles in the circulation. To obtain the total corpuscle volume, it is only necessary to know the volume of an average corpuscle, which can be derived by means of the hematocrit. If the recipient's cells are of a different size from those of the transfused blood, a correction could, of course, readily be made, as the relative numbers of transfused and native cells are known; no correction can, however, be made for any change in the size of the individual corpuscle which may occur as it passes to different parts of the circulation, where it is exposed to different tensions of carbon dioxid. If we proceed to obtain a figure for the total blood volume, the contribution of the hematocrit in determining the corpuscle volume will cancel out;[5] therefore, all we really need to know is that as there are $\frac{C \times C_t V_t}{U_2 - U_1}$ cells in the circulation, and C cells in the unit of blood examined, assuming that the proportion between plasma and corpuscles is the same in the rest of the body, $\frac{\frac{C \times C_t V_t}{U_2 - U_1}}{C}$ will give the number of those unit volumes which measure the total blood of the circulation. C cancels out, and the formula for the whole blood derived from the cell volume is $\frac{C_t V_t}{U_2 - U_1}$. Although, from

5. Let X^t be the volume of the corpuscles in 1 c.mm. of the blood transfused. Let X^p be the volume of the corpuscles in 1 c.mm. of the patient's blood before transfusion. Then $\frac{X^t}{C^t}$ and $\frac{X^p}{C^p}$ will equal the volume of an average corpuscle respectively of the transfused blood and of the patient's blood before transfusion. The hematocrit reading of the patient's blood after the transfusion will be: $\frac{\frac{X^t}{C^t} \times (U_2 - U_1) + \frac{X^p}{C^p} \times (C - [U_2 - U_1])}{1}$

and the average volume of a corpuscle in the patient's circulation after the transfusion will be: $\frac{\frac{X^t}{C^t} \times (U_2 - U_1) + \frac{X^p}{C^p} \times (C - [U_2 - U_1])}{C}$

Since the total number of corpuscles in the circulation are: $\frac{C^t V^t}{U_2 - U_1} \times C$

the total corpuscle volume will be:

$$\frac{C^t V^t}{U_2 - U_1} \times C \times \frac{\frac{X^t}{C^t} \times (U_2 - U_1) + \frac{X^p}{C^p} \times (C - [U_2 - U_1])}{C}$$

and the whole blood volume which is obtained by multiplying the corpuscle volume by 1 over the hematocrit reading, will be $\frac{C^t V^t}{U_2 - U_1}$

a casual consideration of the matter, it might seem that by substituting corpuscles for vital dye, I am simply introducing another method for measuring plasma volume, it will, I believe, be seen, on more careful consideration, that it is in reality a corpuscle volume method, as $\frac{C \times V_1}{U_2 - U_1}$ depends on the total number of corpuscles in the circulation, irrespective of their distribution.

LENGTH OF TIME THAT ALL THE TRANSFUSED CORPUSCLES REMAIN IN THE CIRCULATION

In any blood volume determination involving the injection of some substance distinguishable in the circulation, and the determination of its degree of dilution, the relative length of time before which an appreciable amount of the substance is lost from the circulation is a matter of importance. In my opinion, all the unlike group corpuscles, as a rule, stay in the circulation for from two to three weeks, sometimes longer. Apparently, they are in part eliminated by a certain physiologic state of the recipient, after which those escaping destruction remain in the circulation until removed by another crisis of elimination. The evidence for this conception has been given elsewhere.[4] Although, in some patients, there is an initial fall in the count of the transfused corpuscles, there is reason to assume that it is due to an increase in the blood volume, and not to elimination of transfused corpuscles. These drops in the count have generally occurred either in patients who have received transfusions because of loss of blood and shock resulting from operation, and whose initial blood volumes have been low, as calculated by this method; or in patients with pernicious anemia whose first blood volumes have been low, but later, with evidence of improvement, have been apparently increased. Furthermore, the blood volume did not decrease beyond a point which would be consistent with dilution caused by the establishment of a probable blood volume as determined by the method of injection of vital red. As there were many instances in which the count of the transfused corpuscles was maintained at approximately the some level after transfusion, it would seem practically certain that when these initial drops in the count occur, they are due to blood volume adjustment, and that there is no elimination of the transfused corpuscles until one of these abrupt and marked changes in the count occurs. The findings in two cases of pernicious anemia that I have had the opportunity to study intensively for a long time are tabulated in Table 1. The constant counts for twenty-eight and thirty-one days, respectively, are shown, after which, within from two to three days, a fall occurred, and the count remained approximately constant at a lower stage for thirty-one days, in one instance, and for fourteen days, in the other, as long

as the patient was under observation. Determinations were made from blood taken from the ear.

TABLE 1.—*Cases of Pernicious Anemia, Showing no Loss of Transfused Blood for a Month, with Subsequent Steplike Fall in Count*

Case 244, patient in Group 2 who received transfusion of 500 c.c. of Group 1 blood and Group 2 transfusion on the seventh, forty-ninth and fifty-fifth days after the Group 1 transfusion

Days After Transfusion	Total Red Cell Count	Count of Unagglutinated Corpuscles
0	3,080,000	645,000
3	2,960,000	616,000
6	2,810,000	629,000
8	3,280,000	621,000
11	3,220,000	608,000
13	3,430,000	702,000
15	2,990,000	631,000
17	3,050,000	621,000
19	3,140,000	644,000
21 (patient felt better)	2,920,000	593,000
22	2,770,000	616,000
24	2,940,000	638,000
26	2,780,000	623,000
27	2,940,000	597,000
31	2,940,000	652,000
34	2,820,000	451,000
36	2,750,000	557,000
38	2,800,000	542,000
56	3,180,000	513,000
58	3,480,000	509,000
60	3,260,000	467,000
62	2,990,000	467,000
64	3,300,000	519,000
68	3,300,000	479,000
69	3,080,000	451,000
71	3,010,000	428,000
73	3,110,000	372,000
75	3,010,000	377,000
77	3,210,000	385,000
79	2,920,000	421,000

Case 214, patient in Group 2 who received a Group 1 transfusion and five Group 2 transfusions while under observation

Days After Transfusion	Total Red Cell Count	Count of Unagglutinated Corpuscles
5	1,150,000	328,000
7	1,490,000	437,000
10	1,470,000	362,000
12	1,750,000	360,000
14	1,610,000	333,000
17	1,810,000	380,000
19	2,050,000	340,000
21	1,910,000	380,000
24	2,130,000	327,000
26	2,200,000	317,000
28	2,850,000	339,000
31	2,770,000	277,000
33	2,910,000	267,000
35	3,030,000	280,000
38	2,360,000	255,000
42	2,270,000	245,000
45	2,370,000	221,000

Wearn,[6] however, who has used my method of determining the length of life of the unlike group transfused corpuscle, in a series of patients

6. Wearn, J. T.; Warren, Sylvia; and Ames, Olivia: The Length of Life of Transfused Erythrocytes in Patients with Primary and Secondary Anemia, Arch. Int. Med. **29**:527-538 (April) 1922.

with pernicious anemia, and in another series with nephritis, considers that the transfused cells show a "steady gradual disappearance from the circulation of the recipient," but his data do not seem to me to support this conclusion. As he himself admits, the majority of his cases were observed at intervals too far apart to decide this point; then, too, the type of case chosen is one in which the vital red method has disclosed considerable capacity for volume variation. In the case of a patient with pernicious anemia, one of his most intensively studied cases, and one in which the transfusion was sufficiently large so that the fluctuations in the count of transfused corpuscles would not be within the error of the technic, there was a very definite indication of the steplike progress of elimination. Six hundred cubic centimeters of Group 1 (Group 4, Moss) citrated blood was transfused into a patient in Group 2; immediately afterward, the count of unagglutinable corpuscles was 530,000, while that taken thirty-one days later was 553,850; forty-eight days after transfusion, the count was 349,800, and fifty days after this reading, during which time certain irregular changes in the count occurred, one of which was, I believe, due to icebox incubation, the count was 351,450. Similarly in Case G, the first count of unagglutinable corpuscles, taken two days after transfusion, was 253,000; twenty-eight days after transfusion, it was 265,650. The next count, taken three days after this, was 163,350; that eighteen days later was 130,550. In Wearn's two cases of pernicious anemia, B and C, there was an initial fall of the count, which, judging from the amount of blood injected and the degree of the fall, might well have been due to improvement in the blood volume, as afterward the counts stayed on a level for considerable time. Of his nephritis cases, Case H would seem to me to be the only one that offers any evidence of continuous elimination of the transfused blood corpuscles, and, according to the proctocol, there was a continuous loss of blood in the urine, which, in the course of sixty days, may have been sufficient to affect the number of transfused corpuscles. However, the amount of blood transfused, 250 c.c. diluted with citrate solution, was so small that it would be unwise to place much significance on the counts of transfused blood. His most significant case was Case A, because it was the most intensively studied and because a larger amount of blood was given; and yet this case does not substantiate the contention of a continuous and gradual elimination. If, as I believe, none of the transfused corpuscles, as a rule, leave the circulation for from fourteen to twenty or more days, this method is good for a prolonged study of blood volume changes. When doubt arises as to whether elimination of transfused corpuscles or increase in blood volume has occurred, the point must be checked by the parallel use of another method.

CONSISTENCY OF THE AGGLUTINABILITY OF THE RECIPIENT'S CORPUSCLES

As this blood volume method is designed to be used over a considerable length of time, besides knowing something about the probability of elimination of the transfused blood, it is also necessary to know the probabilities of any change occurring in the agglutinability of the corpuscles of the recipient. The completeness of agglutination of the

TABLE 2.—*Effect of Change in Concentration of Corpuscles on Unagglutinable Residue, U_1, of Pure Agglutinable Blood Sample, the Same Agglutinating Serum Being Used for all Bloods*

	Degree of Dilution		Count of Unagglutinated Corpuscles in 1 Mm.	Original Count of Blood
Blood Showing No Effect of Concentration of the Corpuscles on U_1	Blood	Serum		
Blood 1	1	55	2,050	1,770,000
	2	55	2,050	
	4	55	2,250	
	5	55	2,500	
Blood 2	2	55	1,800	1,510,000
	5	55	2,150	
Blood 3	1	55	550	4,500,000
	2	55	600	
	4	55	550	
	6	55	500	
Blood 4	1	55	1,300	5,000,000
	2	55	800	
	4	55	1,350	
	6	55	1,300	
Blood 5	1	55	2,000	5,390,000
	2	55	1,600	
	4	55	1,600	
	6	55	1,700	
Blood Showing an Effect of Concentration of the Corpuscle on U_1				
Blood 6	1	55	600	4,480,000
	2	55	1,500	
	4	55	2,800	
	6	55	5,600	
Blood 7	2	55	1,700	2,240,000
	5	55	5,500	
Blood 8	2	55	3,850	3,800,000
	5	55	6,500	

recipient's corpuscles depends partly on the potency of the serum used, and partly on a quality inherent to the corpuscles. Certain serums will agglutinate pure blood of an agglutinable type with a smaller residue of free corpuscles than will others. The potency of the serum can readily be checked, and, as iso-agglutinins are quite stable, it is often possible to use the same serum throughout a series of experiments. The possibility of change in the agglutinability of the recipient's corpuscles, however, called for investigation. It was necessary to know whether, as a result of a change in the condition of the patient, any change in the agglutinability of his corpuscles occurred, and also what error was introduced on an improvement or drop in his cell count by the increase or decrease in the number of his corpuscles, or, which involves the same point, what correction should be made for the unagglutinable count of the

patient's own corpuscles, U_1, when because of too great a density of the transfused corpuscles for convenience in counting, a further dilution with serum is necessary.

It would appear from a study of the unagglutinable residue of blood unmixed with corpuscles of an unagglutinable type that the agglutinability of the recipient's corpuscles is peculiar to the individual; it may change, but usually does not even in as long a period as a year, and that for the majority of bloods the number of cells free after agglutination does not depend on the density of the suspension agglutinated.

In five instances (Table 2), on varying the amount of blood agglutinated with a given amount of serum, the number of free corpuscles remained the same. The mechanism suggested, in these cases, was that which determines the dissolved fraction of a comparatively insoluble salt in the presence of an excess, rather than the differential agglutination of the more agglutinable corpuscles of a not entirely homogeneous mixture. In three bloods, on the other hand, this was not the case. These bloods, which, compared with the others, gave a high count of unagglutinable corpuscles, showed a variation in the number of free corpuscles as the amount of blood per unit volume of serum was changed. This may have been due to the presence of unagglutinable cells, of which there were more in the richer mixtures of blood, as suggested by the work of Isaacs,[7] but as I have not found the cells described by Isaacs to be unagglutinable by my technic, I consider it more likely that the corpuscles, in these instances, were uniformly weakly agglutinable to such a degree that the mechanical manipulation necessary for making the count became a factor and loosened a greater number in the specimens with more clumps present. The findings are listed in Table 2.

Of twelve subjects whose blood was studied for agglutinability over intervals ranging from one day to a year, nine showed a consistency in the count of unagglutinated corpuscles which came within the error of the technic. The majority of these were patients with pernicious anemia, receiving a series of transfusions; one was a normal donor whose blood was tested before hemorrhage, and three days later. Of the three patients who showed variation, the blood of Mrs. S., which had a high count of unagglutinable corpuscles, showed an increase in agglutinability when the patient had an attack of pneumonia, with a return toward the high count on her recovery. The two marked exceptions were found in two patients whose counts were taken simultaneously a month apart; in one of these, there was an increase in the count of unagglutinable corpuscles, and in the other a decrease (Table 3).

7. Isaacs, Raphael: Properties of Young Erythrocytes in Relation to Agglutination and Their Behavior in Hemorrhage and Transfusion, Arch. Int. Med. **33**:193-209 (Feb.) 1924.

The practical result of these observations is that, after an unlike group transfusion, the probabilities are that the agglutinability of the recipient's corpuscles will not have changed, and that a true figure for the number of unagglutinable corpuscles introduced by the transfusion will be obtained by substracting the count of unagglutinable corpuscles made

TABLE 3.—*Illustrations of Degree of Stability of U_1, Residue of Unagglutinated Corpuscles of an Agglutinable Blood, Observed in Patients Over Varying Lengths of Time When Group 1 Serum Was the Agglutinating Medium*

Case	Date	Red Cell Count	U_1	Notes
23	1/ 4/19	.....	80,000	
	12/ 8/19	830,000	70,000	
97	10/ 7/19	1,900,000	70,000	
	4/ 2/20	2,080,000	87,000	
	9/ 2/20	2,240,000	70,000	Splenectomy, Aug. 5, 1920, followed by transfusion
155	5/ 9/21	1,480,000	18,700	Patient in Group 4, receiving Group 2 transfusions
	5/16/21	2,380,000	14,000	
Dr. W.	2/24/20	4,290,000	71,000	
	2/26/20	4,120,000	62,000	
	2/28/20	3,450,000	66,000	
	3/ 3/20	3,450,000	71,000	
	3/ 5/20	2,720,000	74,000	
J. H.	2/ 8/21	1,160,000	55,000	Before transfusion
	2/ 8/21	1,880,000	58,000	After transfusion
	3/ 2/21	1,310,000	43,000	
	3/ 3/21	1,760,000	49,000	
Mrs. B.	2/ 4/21	1,920,000	53,000	Before transfusion
	2/ 4/21	2,000,000	40,000	After transfusion
N.	2/20/24	1,510,000	47,000	Receiving a series of transfusions
	3/21/24	1,980,000	69,000	
A.	2/20/24	2,240,000	102,000	Receiving a series of transfusions
	3/21/24	3,510,000	113,000	
Mrs. S.	2/ 4/21	1,810,000	101,000	Before transfusion
	2/ 4/21	2,360,000	98,000	After transfusion
	2/ 7/21	2,330,000	76,000	
	2/13/21	2,280,000	96,000	
	2/14/21	1,890,000	50,000	
	2/15/21	.....	45,000	Had pneumonia
	2/26/21	3,250,000	77,000	
J. C.	2/26/21	.....	28,000	Professional donor
	2/29/21	.....	11,000	Three days after loss of 500 c.c. of blood
C.	2/20/24	3,810,000	128,000	
	3/21/24	3,940,000	79,000	
B.	2/20/24	1,770,000	40,000	Transfusions
	3/21/24	2,890,000	102,000	

by the same technic before transfusion from the count of unagglutinable corpuscles made after transfusion. If, in the meantime, the patient's blood count has changed, the probabilities of error will be less, if no account is taken of the change in making allowance for the native unagglutinable cells. When, because of too great a density of the transfused unagglutinable corpuscles, it is difficult to make the count and it becomes necessary to dilute the specimen, as taken by the usual technic, with serum, before subtracting the initial count of the recipient's unag-

glutinated corpuscles from the total count, the initial count should be multiplied by the amount of the dilution of the specimen.

A COMPARISON OF COUNTS MADE ON BLOOD FROM THE EAR AND FROM THE VEIN

In a series of comparisons of red blood counts made from the ear and from the basilar vein, it was found that the counts of blood from the ear might be higher or equal to the counts from the vein, but that they were usually higher; very exceptionally were they lower. This was true in normal subjects and in patients with pernicious anemia. The range in the absolute difference in the counts in the patients with pernicious anemia was equal to that in the normal subjects, being from 0 to about 80,000 corpuscles for each cubic millimeter of blood; the percentage difference in the patients was, of course, because of the low red blood counts, very much greater in this group. The fact that the range of absolute difference is similar in the two groups suggests that this increase in the capillary count over the venous count may not be a function of the blood, for if the difference were due to a change in the proportion of corpuscle and serum, it would be much greater in the normal blood. It would seem probable that it is a function of something which is more equal in the two types of cases. This common factor is likely to be capillary volume. It seems to me that on cutting tissue, certain of the capillaries may go into the expanded condition of shock and permit the passage of fluid through their walls, thus becoming packed with corpuscles, as described by Krogh.[8] The slight milking, employed to obtain the drop of blood for the count, would be expected to dislodge these and increase the count taken from such a cut over that taken from the vein. The fact that duplicate counts from the ear have proved to be more irregular than can be explained on the basis of error in the technic of dilution and counting, as judged from the percentage of error found in the work of the same technician in duplicate counts of citrated blood, would seem to indicate that the error lies in the process of obtaining the blood. Since I believe it highly probable that a count of blood taken so that it includes blood obtained from injured capillaries may not be a true index of the corpuscle content prior to injury, I consider it very desirable to obtain the count from venous blood.

SUMMARY AND CONCLUSION

A method for determining blood volume is described, based on the degree of dilution of transfused Group 1 (Group 4, Moss) blood in a recipient of another group.

8. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922.

It is shown that the whole blood volume obtained by this method is dependent on circulating corpuscle volume. On this account, the results obtained by it would constitute a check on whole volume calculations based on plasma volume determinations.

The method is advocated as a means of studying blood volume changes.

ASTHENIA AS A CHIEF COMPLAINT IN CARCINOMA OF THE STOMACH *

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That the subject of gastric carcinoma is a paramount one must be evident to all. About one half of all cancers occur in the stomach. Martin [1] found that 0.47 per cent. of all hospital admissions are for gastric cancer. Ewing [2] similarly emphasizes the great frequency of this tumor: "The stomach is probably the most frequent seat of cancer in the male, as the uterus is in the female." Whether the condition numbers one third or one half of all neoplasms is not essential, but it does demonstrate the tremendous importance of early recognition. Modern medicine and surgery avail little. Whereas our laboratory aids have advanced, our clinical intuition has lagged behind, and so we find that the diagnosis of gastric carcinoma is still terribly hopeless. Hence, any clinical means that may aid the internist or laboratory man in making an earlier diagnosis must be of distinct value.

In the study of this subject, one finds that the usual textbook descriptions have been handed down from author to author. Similarly, the clinician in the diagnosis of peptic carcinoma keeps in mind the picture of an old man with a palpable tumor, cachectic, vomiting and with anacidity.

Before these symptoms and findings become outstanding, there must have been a period of growth when there were none or, at the most, few symptoms; so, too, before the roentgenologist finally examines the patient and discovers a large defect, there must have been a time when a small lesion was present. It is with the hope that carcinoma of the stomach will be suspected earlier in certain types of cases that this paper is presented. The type referred to is the case in which gastro-intestinal symptoms are entirely lacking, or, if present, occur to a minimal degree. In fact, one can usually obtain more or less indefinite gastro-intestinal complaints in any individual between 40 and 60, especially if he is ill. The patient who has gastro-intestinal complaints in the foreground is the classical type, the one described in books and taught in the medical school. It is the other type, less frequent, more difficult of recognition but none the less important, with which we are concerned. In fact, one author [1] goes so far as to state, "One general rule holds in

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1. Martin C. F.: Carcinoma of the Stomach, in McCrae, Osler, Modern Medicine **3**:264.

2. Ewing: Carcinoma of the Stomach, in Neoplastic Diseases, Ed. 2, p. 624.

most cases, viz., the absence of all gastric symptoms and signs is important evidence against cancer." With this statement the facts of this paper differ entirely.

The following is the first case of gastric carcinoma in which the history revealed absolutely no gastric symptoms and in which weakness was the chief complaint or signal symptom.

CASE 1.—A Russian, aged 56, married, a waiter, was admitted, Jan. 5, 1922, and discharged January 25, with the diagnosis of carcinoma of the stomach (inoperable). The condition was unimproved.

His chief complaint was weakness, which had persisted for the last six months. He had been told some time previously that he suffered from kidney trouble. However, he had no dysuria, no nocturia or hematuria, only frequency. His present illness commenced about six months before admission, with a feeling of weakness. This weakness progressively increased until about one week before admission, when it became so marked that the patient was forced to discontinue work and go to bed. No gastric symptoms, no nausea or vomiting and no jaundice were present. His appetite was fair; he was mildly constipated. He never noticed bloody or tarry stools, and there was no known loss of weight.

Physical examination showed a poorly developed and poorly nourished middle aged man. Physical examination was negative, except for a marked, yellowish pallor of the mucous membranes and the skin. A small, lipomatous mass was found near the left nipple. The deep reflexes were hyperactive.

Because of the pallor, complete routine blood tests were performed. The bleeding and coagulation time were normal. The blood count showed: 52 per cent. hemoglobin; 3,160,000 erythrocytes (0.83 color index); 10,000 leukocytes; 72 per cent. polymorphonuclears; 18 per cent. lymphocytes, and 10 per cent. monocytes. Slight anisocytosis and poikilocytosis of red cells were present. Blood platelets numbered 106,000. The blood pressure was 145 systolic, 65 diastolic. The Wassermann test was negative. The phenolsulphonephthalein test resulted in the return of 24 per cent. dye excretion in two hours. The stools were found positive for occult blood. The roentgen-ray examination of the gastro-intestinal tract showed evidence of a neoplasm on the posterior wall and lesser curvature, just below the cardia. It seemed quite extensive. The pyloric half of the stomach showed no abnormality. Peristalsis in the area was normal. Surgeons considered the case inoperable.

Apparently, the cardia and pyloric orifices were patent, peristalsis was normal and no retention was present; hence, there were no gastric symptoms. This is the usual type in which weakness is the chief complaint, and in which gastro-intestinal symptoms are entirely absent or negligible.

The second patient was a man who entered the hospital for an acute inflammatory condition of the eyelid, but whose fundamental complaint was weakness.

CASE 2.—A peddler, single, admitted, May 15, 1923, and discharged, August 22, with the diagnosis of carcinoma of the stomach, was admitted to the eye service with a complaint of pain and swelling about the right eye which he had had for eight days. He had had gonorrhea fifteen years before, with a "touch of chancre" at the same time. For six months, he had been feeling weak and run down, and occasionally suffered from dizzy spells.

Physical examination showed an acutely ill man, aged about 45, with lemon colored skin and swelling and redness of the right eye, the lids being almost closed. Red streaks extended along the forehead. The optic nerve heads were pale. The teeth were in poor condition. The tongue was glossy, smooth and atrophic. A large "spleen" was palpated in the left hypochondrium, four fingers below the costal margin, extending to the epigastrium.

The provisional diagnosis was orbital cellulitis with spreading lymphangitis (cavernous sinus disease? tabes?).

The right upper and lower lids were incised, and pus was evacuated. The visual fields were found to be normal. The blood pressure was 110 systolic, 55 diastolic. A diagnosis of splenomegalic cirrhosis was made because of the large liver and spleen. The glossy tongue was ascribed to syphilis.

The patient was transferred to the medical side of the hospital. The blood count was: 34 per cent. hemoglobin; 3,184,000 red blood cells (0.53 color index); 19,200 white blood cells; 68.5 per cent. polymorphonuclears; 2.5 per cent. eosinophils; 0.5 per cent. basophils; 20 per cent. lymphocytes; 7 per cent. monocytes, and 1.5 per cent. myelocytes. The blood platelets totaled 450,000. The stool was positive to the quaiac test for blood. No free hydrochloric acid was found in the fasting or the Ewald test meals. The urine was constantly negative. The blood and the spinal fluid Wassermann tests were negative. The roentgen-ray examination of the stomach showed the presence of a large defect, involving almost the entire upper two thirds of the stomach. This observation indicated the presence of a new growth.

The third case was that of a man whose first discharge diagnosis was atherosclerosis and whose chief symptoms were weakness, chest pain and dyspnea, with no or only negligible gastric complaints. He was discharged improved, and then returned. No one suspected a gastric condition.

CASE 3.—A Russian, aged 52, a tailor, was admitted Dec. 3, 1923, and discharged December 20, with a diagnosis of carcinoma of the stomach. His chief complaint was weakness, which had persisted for nine months. The patient had always been healthy until nine months before, when he suddenly fell unconscious while walking in the street. After this, he remained in bed for nearly two months because of weakness. This weakness increased so that, for six months, he could not walk. On attempting to walk, he became very pale, complained of precordial distress and felt as though he were about to die. For the previous five months, he had had constant pains all over the abdomen; this pain bore no relation to meals, and was relieved somewhat by bowel movement. During this time, he was slightly constipated. Seven months before, he had had gaseous eructations, and had vomited. The stools were normal in color; there was no hematemesis, no jaundice. His appetite was poor, and he had lost much weight. Physical examination showed him to be an underdeveloped, undernourished old man, chronically ill, yellow, with an edematous sacrum and scrotum. The pupils were slightly irregular; a marked arcus senilis and tortuous blood vessels were present. The supraclavicular fossae were sunken. The heart was moderately enlarged to the left, with a low pitched, blowing, presystolic, systolic murmur at the apex and mitral area. The blood vessels were thickened. Liver dulness was increased.

The systolic blood pressure was 120; the diastolic, 60. The stools showed occult blood. The blood count was 38 per cent. hemoglobin; there were 3,000,000 erythrocytes (0.63 color index), 13,000 leukocytes, 85 per cent. polymorphonuclears, and 15 per cent. lymphocytes.

Gastric analysis showed absent hydrochloric acid and diminished total acids in the fasting and Ewald test meals. The urine was negative except once, when a trace of sugar was found. Roentgen-ray examination of the gastro-intestinal

tract showed the gastric tone and peristalsis to be normal. There was a suspicion of a small defect on the posterior wall in the region of the cardia, just to the left of the cardiac opening. Sigmoidoscopy, December 17, revealed an obstructive extracolonic mass at the level of the second fold of Houston. The final diagnosis was carcinoma of the cardia with metastases to the peritoneum and to the culdesac of Douglas in a patient previously discharged from the hospital with a diagnosis of arteriosclerosis, and who had returned to the hospital because of weakness.

These three cases led to an investigation of the cases of carcinoma of the stomach on the medical side for the years 1923, 1922 and 1921, in which there were, at the onset or throughout the course of the case, no gastro-intestinal complaints, or in which these were in the background. Asthenia was a complaint months before a diagnosis of gastric cancer was made.

Case 4.—A patient, aged 60, examined, July 10, 1923, had as chief complaint weakness of two years' duration; his symptoms, for the previous two months had been aggravated by coughing. Swelling of the ankles was noted. The laboratory findings, i. e., the Ewald test meals and the roentgen-ray examination, were characteristic of stomach carcinoma. A defect was found in the posterior wall and along the lesser curvature of the body of the stomach.

Case 5.—A man, aged 44, was in perfect health until a few months previous to June, 1923, when he lost appetite and strength. He had no other gastro-intestinal symptoms. The case had been diagnosed as neurasthenia and overwork, and he had been sent to Florida. An exploratory laparotomy disclosed an inoperable cancer of the stomach with liver metastases.

Case 6.—A man, aged 62, was absolutely symptomless until two days before admission in September, 1923, when he entered the hospital because of a hemorrhage and weakness. Roentgen-ray examination gave evidence of a small defect on the posterior wall of the stomach in the region of the cardia.

Case 7.—A man, aged 64, whose signal complaint was increasing weakness for three months, had lost 35 pounds (15.9 kg.) and complained of anorexia, belching and a feeling of distention after meals. The case was signed out as an inoperable carcinoma of the stomach on the greater curvature.

Case 8.—A man, aged 58, whose chief complaints were weakness, dyspnea and swelling of the feet of five weeks' duration, entered in March, 1922. No loss of appetite, no vomiting, no bleeding and no abdominal pain were present. A fairly large defect on the lesser curvature below the cardia was found.

Case 9.—A man, aged 59, examined in September, 1923, had had increasing weakness for two months. The roentgen-ray examination showed a large defect in the greater curvature of the stomach.

Case 10.—A man, aged 56, whose first symptom was extreme weakness that had commenced one year previous to admission, in January, 1922, and which was associated with anorexia, had lost 28 pounds (12.7 kg.) in the course of the year. There were no gastro-intestinal symptoms except constipation. A subtotal gastrectomy was performed, and the patient was discharged well.

Case 11.—A woman, aged 56, whose signal symptom was weakness for six months, was admitted in January, 1923. The weakness grew progressively worse. Other complaints were palpitation, precordial pain, dyspnea and pallor. She lost about 10 pounds (4.5 kg.). The case was diagnosed as secondary anemia and nephritis. The Rehfuss test showed no free hydrochloric acid, and the roentgen-ray examination demonstrated irregularity in the region of the antrum.

CASE 12.—A woman, aged 55, who eight months before admission, in January, 1921, began to feel weak, was without definite symptoms until four months previous to admission, when she commenced to cough, developed pain in the back, and had dysphagia. A carcinoma of the cardia was found.

CASE 13.—A woman, aged 50, who lost 50 pounds (22.7 kg.) in five years and whose strength had greatly diminished, was admitted in June, 1921. Her complaints were cardiac, i. e., palpitation and precordial pain. There were no tarry stools, jaundice, belching or pyrosis. The Rehfuss test showed blood and an absence of hydrochloric acid. There was no roentgen-ray confirmation in this case.

CASE 14.—A woman, whose chief complaint was gradual weakness of two months' duration, but who had had a sour taste in the mouth for four months, was admitted in October, 1921. There was no vomiting, belching or bloody stools. The bowels were regular. Free hydrochloric acid was absent in the test meal. No roentgen-ray confirmation was made and the patient left the hospital against advice.

CASE 15.—A man, aged 64, who eight months previously had noticed swelling in the feet and progressive weakness, was admitted in September, 1921. The Rehfuss test proved the absence of free hydrochloric acid and the presence of lactic acid. Roentgen-ray examination showed a defect involving the pyloric end of the stomach.

COMMENT

Here is a series of seventy-six medical cases of carcinoma of the stomach in which fifteen patients, or 20 per cent., complained chiefly of asthenia and presented no, or a very mild, gastro-intestinal history. If we exclude Cases 13 and 14, in which absolute confirmation of the diagnosis is lacking, we still find a record of 17 per cent. It is true that the cases were not the type that the surgeon sees, i. e., the typical patient, almost cachectic, with all the classical signs of cancer. They were cases chiefly sent in for diagnosis.

The complaint of asthenia so common here was not the asthenia of cachexia. That symptom, of course, would be worthless. On the contrary, the complaint was comparable to asthenia of early pulmonary tuberculosis.

Patients with cancer of the breast, uterus, esophagus or lung do not complain chiefly of weakness. Apparently, it is characteristic in the cases under discussion.

As to the cause of the asthenia, a secondary anemia is common in cancer of the stomach. In fact, extremely important differentials are pernicious anemia, secondary anemia and nephritis. A destruction of the red blood cells occurs, probably due to a toxic agent set up by the neoplasm (one author [3] has suggested that protein and lecithin cause this). The asthenia may directly, rather than indirectly, be due to the infection and ulceration of the tumor. In fact, both the latter conditions

3. Loeper, M.; Faroy, G., and Debray: Anemia with Gastric Ulcer, Progrès. méd. **36**:244 (May 25) 1921; abstr. J. A. M. A. **77**:579 (Aug. 13) 1921.

are quite common in the lesion described. Many authors [4] have noted the simulation of pernicious anemia with symptoms of weakness, numbness and tingling hands and feet and other paresthesias.

The lack of gastro-intestinal complaints can probably be explained on the basis of the location of the growth. When the pyloric and cardiac orifices are involved, gastric complaints are prominent because of obstruction. Some authors even divide "early gastric cancer" into those in which the cancer is situated near the orifices and those that are not. Brown [5] states that the most frequent site is the lesser curvature from whence the growth extends to pyloris, cardia or over the fundus of the stomach. The same author also described three types of gastric carcinoma, one of which is insidious in onset and affects persons of middle life with a singularly uneventful digestive history.

Smithies,[6] in 712 consecutively operated and pathologically proved cases, found that 2 per cent. gave no symptoms whatever.

SUMMARY

In a condition like carcinoma of the stomach, in which the early symptoms are vague and in which, unfortunately, an early diagnosis is extremely essential, one must utilize every means at his command. Not the least of these is the history obtained from the patient.

Asthenia as a signal complaint is not an uncommon symptom of tumor of the stomach, being present in from 17 to 20 per cent. of this series of (medical) cases.

Absence of gastro-intestinal symptoms does not rule out carcinoma of the stomach. The presence of asthenia and anemia, with absence of gastro-intestinal symptoms in a middle-aged person with no apparent cause for the anemia, is an indication for gastro-intestinal roentgen-ray examination. In fact, on this complaint alone, if no cause for the severe secondary anemia can be found, an exploratory laparotomy should be performed. Anemia, secondary or even primary, is a diagnosis which should immediately bring to mind a possible differential diagnosis of carcinoma of the stomach. The anemia, when present, is probably due to destruction of the red blood cells by a substance produced by the new

4. Oliensis, A. E.: Carcinoma of the Stomach Simulating Pernicious Anemia, New York M. J. **114**:298 (Sept. 7) 1921. Houghton, Hallstead and Satterlee: Progressive Pernicious Anemia with Gastric Carcinoma, Long Island M. J., October, 1914, p. 361.

5. Brown, T. R.: Carcinoma of the Stomach, Nelson System of Medicine, **5**:295, 1924.

6. Smithies, Frank: Symptoms and Signs of Gastric Cancer; An Analysis of 712 Consecutive Operatively and Pathologically Proved Cases, J. A. M. A. **64**:8 (Feb. 20) 1915.

growth. The asthenia is due to this anemia, or to the toxic products caused by the infection and ulceration of the growth.

The practically constant subacidity, anacidity or achylia suggests that the absence of the gastric secretions plays an important rôle in the anemia, and hence the complaint of weakness. The association of the same findings in pernicious anemia adds interest to this suggestion.

Cases were presented in which the symptom of weakness preceded by months or years the diagnosis of cancer of the stomach.

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CORRECTION

"The Permeability of Human Blood Cells to Carbon Dioxid and Ammonia Hydroxid in Solutions of Same p_H," Herman E. Pearse, A.B., Boston, March issue, p. 347: The word "later" in the third line should read "latter."

Book Reviews

THE CHEMISTRY OF THE BLOOD IN CLINICAL MEDICINE. By O. L. V. DE WESSELOW. Pp. 252. London: Ernest Benn, Ltd., 1924.

This manual discusses the chemical composition of the blood, acidosis and alkalosis, variations of the blood sugar in health and disease, changes of the blood constituents in nephritis, tetany, rickets, gout, and in certain other conditions, such as anoxemia.

To these discussions are added methods for determining the nonprotein nitrogen constituents of the blood, the chlorids, the carbon dioxid combining power of the plasma, the phosphate and calcium content.

Although the methods given are excellent and the subject matter is well presented, most of these are contained in other more comprehensive laboratory guides.

PATHOGENIC MICROORGANISMS. By PARK and WILLIAMS. Eighth edition, enlarged and revised. Pp. 811; 220 illustrations. Price, $6.50. New York: Lea and Febiger, 1924.

To the students of bacteriology this text needs no introduction. It ranks among the foremost of its kind, and this edition has been brought to date by thorough revisions and extensions. The essential features of bacteriology, the preparation and sterilization of mediums, the characterictics of various pathogenic bacteria, immunity, the protozoan parasites, water and milk sanitation, filterable viruses, and other important features in the realm of bacteriology are fully and excellently discussed. Students and workers in bacteriology will find this an invaluable text.

THE CHEMICAL ASPECTS OF IMMUNITY. By H. GIDEON WELLS. Monograph (American Chemical Society Series). Pp. 254. New York: Chemical Catalog Company, Inc., 1925.

This monograph by Wells has been written not only with the purpose of summarizing the subject matter included by the title but also for serving as a guide to the literature concerned. The introductory chapter states the reasons for regarding immunologic reactions as chemical processes, and defines briefly the terms commonly used. Then follow chapters on antigens, immunologic specificity, the nature of antibodies, the neutralization of toxin by antitoxin, agglutination and precipitation reactions, the lytic reactions, the Wassermann reaction and related reactions with syphilitic serum, anaphylaxis, phagocytic immunity, and resistance to nonantigenic poisons. Each chapter is a concise resumé, and includes a large bibliography. A helpful recapitulation by the author summarizes at the end of each chapter the subject matter presented. Dr. Wells' fine ability to analyze and present a subject such as this makes the monograph especially fascinating to read, and the book should be in great demand by immunologists, chemists and physicians.

PRINCIPLES OF BIOCHEMISTRY. By T. BRAILSFORD ROBERTSON, PH.D., D.SC. Second edition, revised. Price $8.50. Pp. 796; 57 illustrations. New York: Lea and Febiger, 1924.

This text is arranged in six parts. Part I considers the foods, such as the inorganic substances, the carbohydrates, the lipins, the simple and complex proteins, and the hydrolysis, digestion and assimilation of these substances. This part contains much information. The properties of protoplasm are dis-

cussed in Part II. In these chapters are considered the diffusible and colloidal constituents, the physical and chemical properties conferred by these constituents, their variations and interactions. In Part III is considered the chemical correlation through the blood and lymph of the respiratory, digestive and circulatory systems, as well as the general metabolism. Part IV deals with the chemical processes underlying and accompanying life phenomena, such as the energy transformations in living organisms, fertilization and early development, growth, diet, etc. The products of tissue activity are discussed in Part V, and the energy balance of the organism in Part VI.

There is a great diversity of subjects considered in this text of biologic chemistry. To students of medicine, of agriculture and related sciences, as intended, this is a valuable text but it does not contain the large volume of detailed information present in certain other books of this kind, as, for example, the one by Mathews or the one by Hammarsten.

LES RÉSULTATS DU PNEUMOTHORAX THÉRAPEUTIQUE. By DR. PIERRE NAVEAU. Pp. 199. Paris: Amedee Legrand, 1925.

This is a statistical review of the results observed during a period of twelve years in 1,195 patients (service of Dr. Rist). In 817 of this number, pneumothorax was produced; with the other 378, the attempted collapse of the lung was unsuccessful, or the patients refused the treatment. There is no description of the technic employed. The patients treated are arranged in two groups, those nontuberculous and those tuberculous. Among the first mentioned are those with bronchiectasis, gangrene of the lungs, and interlobar or pulmonary abscess. The results among these seem good except with gangrene. With tuberculous patients, pneumothorax favors healing of the pleura. In bilateral tuberculosis, only a small number were benefited. The treatment seems to be helpful when only one lung contains active lesions. Of 534 patients with fibrocaseous tuberculosis, 48 per cent. are well or improved; 17 per cent. are stationary, and 35 per cent. are worse or dead. Among the patients in whom pneumothorax was not accomplished, 81 per cent. of those refusing treatment and 62 per cent. of those in whom adhesions prevented collapse are dead. Considerable space is given to detailed clinical briefs of patients.

THE DIAGNOSIS AND TREATMENT OF RENAL DISEASES. By HUGH MACLEAN, M.D., D.Sc. Second edition. Philadelphia: Lea and Febiger.

According to the author's preface, the book "is intended principally for the general practitioner who feels the need of a short practical account of some of the newer methods employed in investigating renal function." The author has accomplished his purpose in a clear, concise and interesting manner. He is in an unusual position to do this since he has the point of view both of the investigator and the clinician of vast experience in this special field.

The accepted theories of renal function are discussed in relation to the actual findings in acute nephritis and in chronic nephritis, both of the azoremic and the hydremic types. Along with the changes in the urine, blood and tissues are given the findings relative to nitrogen, salt and water retention.

Histologic observations are presented and illustrated by colored plates. The significant remark is made "that the toxin causing the purely degenerative lesion of the kidney (tubular degeneration and hydremic type) may be different from that causing degeneration associated with inflammatory phases (interstitial changes and azotemic type)."

A chapter is devoted to the significance of albuminuria in which the differentiation is made between so-called physiologic albuminuria, albuminuria of adolescents and albuminuria of nephritis. In regard to the last, the statement is made that albuminuria even with casts may not indicate kidney disease, and that albuminuria even after acute nephritis may not indicate progressive renal disease.

The methods and results of blood examinations in renal disease are given in a manner easily understood and readily employed by any enterprising physician. Then other tests for investigating renal function follow: the urea concentration test; the diastatic test; the phenolsulphonephthalein test; Ambard's coefficient of urea excretion; the urea concentration factor, and the chlorid concentration test.

The later chapters concern themselves with the relation of nephritis to blood pressure and cardiovascular changes, the examination of patients for renal efficiency, kidneys in surgical conditions, and the dietetic treatment of nephritis (especially as regards protein).